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# APICAL TUBERCULOSIS

## A Roentgenological Technique for Its Early Recognition with Some Pathogenetic Applications

ABRAHAM J. FLAXMAN<sup>1,2</sup>

Apical tuberculosis arises as a small caseous pneumonic lesion which may spread gradually, for a short time, with concomitant fibrosis. In the great majority of cases, the small acinous focus of caseous pneumonia is soon overshadowed by the proliferative changes, the lesion thus becoming arrested, the remaining caseous portions usually also becoming fibrosed. These lesions commonly do not give rise to symptoms, clinical knowledge of their presence being obtained through roentgenography. These arrested lesions have been termed latent apical tuberculosis, because there are embedded within some of them encapsulated caseous foci containing viable bacilli which, under certain conditions, may undergo reanimation with further progression of the lesion.

The great frequency with which these fibrotic areas ("scars") are found at autopsy in the apical portion of the upper lobes is an undisputed fact. That these scars are all of tuberculous origin and the result of reinfection is not undisputed; but as Jaffe (4) states: "I could convince myself that the majority of the grossly noncharacteristic scars show sufficient microscopic evidence in favor of their tuberculous origin." Compared with their anatomical frequency, however, the incidence of their visualization in the routine anterior roentgenogram of the chest is very small.

When the anatomical localization is correlated with the routine chest technique, the paucity of roentgenological visualization becomes understandable. These fibrotic areas show a predilection for the dorsal portion of the pulmonary apices. They may be present in the pleura (apical caps) with or without an associated narrow layer of subpleural lung tissue; they may be present within the parenchyma, often with the formation of emphysematous areas; or they may be so small as to be recognized only microscopically. In the routine anterior roentgenogram of the chest, however, the dorsal portion of the pulmonary apices is farthest from the film. This factor, as well as the juxtaposition or even overlapping of the posterior portions of the upper ribs, makes roentgenological visualization of these fibrotic areas an uncommon occurrence, their presence being noted only when they are situated in the ventral portion of the apices or, if situated dorsally, when of large size.

The roentgenological visualization of the smaller areas of fibrosis and emphysema may be brought about in the vast majority of cases by a technique which corrects the causes of failure of the routine anterior chest position; namely, by bringing the dorsal portion of the lung apices closer to the film and by separating the projections of the posterior portions of the upper ribs. The posterior lordotic

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position provides such a technique. Following the technique as usually described (9), the cassette is supported by a vertical holder which is adjusted to the proper height for the patient; the latter stands with his back to the cassette, hands on hips, shoulders against the cassette holder, feet about one foot forward, knees slightly bent, abdomen protruding in a position of lordosis; the central ray is projected horizontally and directed to the centre of the cassette. This position brings the dorsal apical region into contact with the cassette and tends to project the upper ribs in a less oblique plane. Furthermore, because of the rotation of the chest about its transverse axis, lesions in the ventral apical region are projected upward, thereby overlying the shadow of the cupola, whereas lesions in the dorsal apical region are projected downward, thereby being brought into clearer view.

The objections to this procedure are that there occurs an apical-diaphragmatic foreshortening of the lung fields which produces considerable exaggeration and distortion of the lung markings and that the upper ribs are not projected in a completely horizontal plane. The distortion of the markings in the apical region may be diminished to a negligible quantity by the following modification in procedure (3): The tube is first centered to the cassette in the customary manner; then it is tilted  $5^{\circ}$  upward from the horizontal and lowered (about 4 inches) until the central ray is again centered to the cassette. The improvement in the appearance of the markings in the apical region is due to the smaller effective focal area brought to bear upon this region. This modification also assists in projecting the upper ribs in a more horizontal plane, since it projects the anterior portions of the ribs upward to a greater extent than the posterior portions. Comparison of productive and exudative infiltrations seen in an anterior roentgenogram with their appearance in the modified posterior lordotic view (figures 3 and 4, and figures 5 and 6) reveals that the distortion in the latter view is negligible; all shadows, however, are "softer" in appearance.

The appearance of normal apices in the posterior lordotic view is shown in figure 1. It is seen that the parenchyma has a sharp upper border and that the vascular shadows extending from the upper pole of the hilar region end sharply about one-half inch below this border. The areas of fibrosis and emphysema observed anatomically are visualized in the posterior lordotic view as soft productive infiltrations and variously contoured "hollow forms" situated craniad to the terminations of the vascular tree (figure 2).

The above technique has a number of important applications:

(1) This method of visualization of small apical fibrotic areas is the earliest roentgenological evidence of tuberculous reinfection. In cases in which the anterior chest roentgenogram (figure 3) reveals a productive infiltration in the apical region, the posterior lordotic view (figure 4) usually visualizes one or more smaller and softer productive infiltrations and/or hollow forms situated craniad to it, indicating the downward progression of the reinfection phase. The attention centered on visualization of an infraclavicular infiltrate is due not only to the fact that it is an acute process which may go on rapidly to tissue necrosis, but also because of the belief that it is "in the infraclavicular region that the progression



FIG. 1. (Top) Posterior lordotic view. Normal apex.

FIG. 2. (Bottom) Posterior lordotic view. Arrows indicate small areas of fibrosis and a "hollow form."

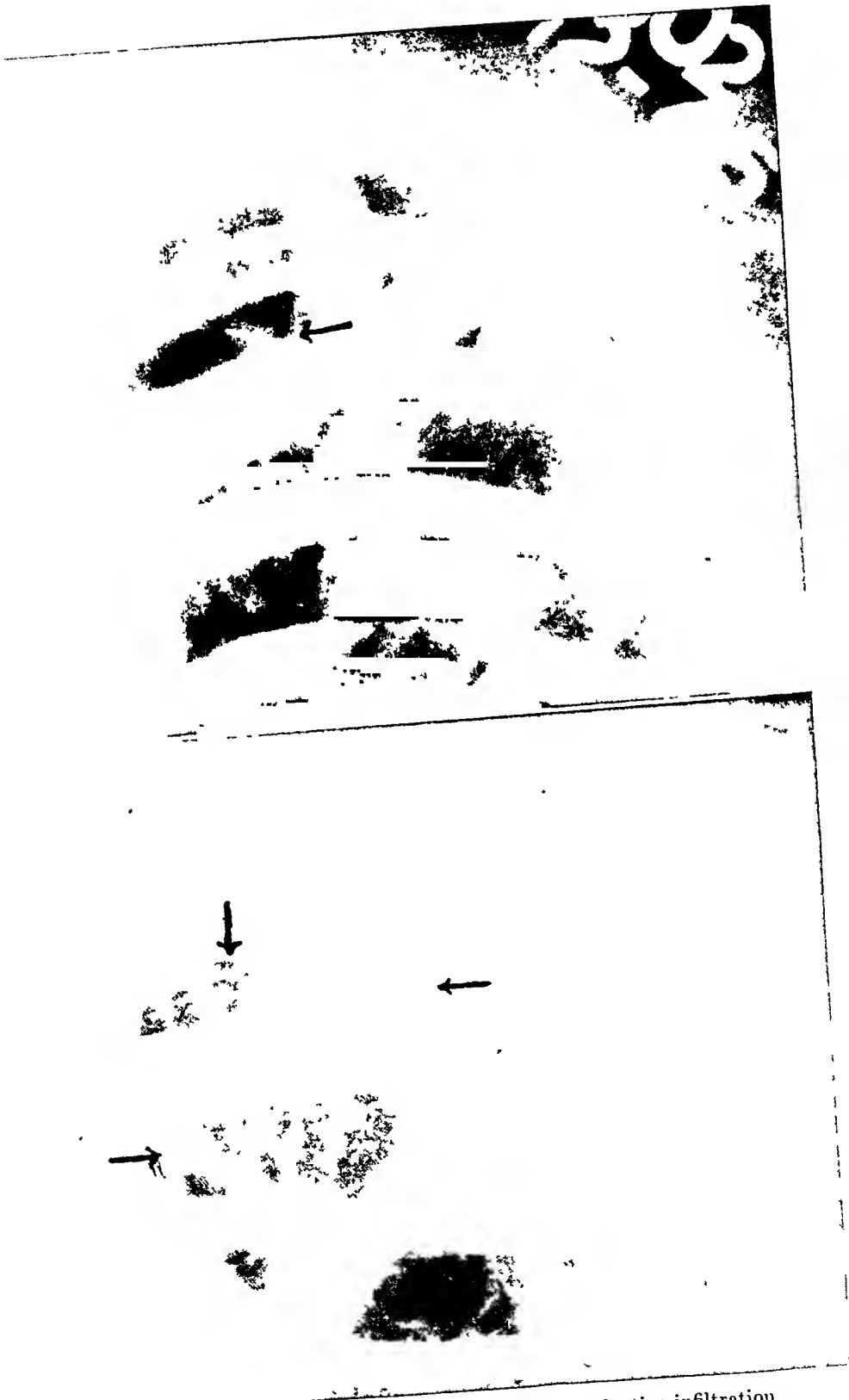


FIG. 3. (Top) Routine anterior view. Arrow indicates a productive infiltration  
 FIG. 4. (Bottom) Posterior lordotic view. Arrow on reader's left indicates the productive infiltration seen in figure 3. The other arrows point to "hollow forms"

of apical tuberculosis first becomes roentgenographically demonstrable" (5). The use of the posterior lordotic projection, however, often enables an earlier demonstration both of tuberculous reinfection and of apical progression. It is therefore suggested that this technique be employed in those instances wherein the purpose is to determine the presence of reinfection rather than clinically significant tuberculosis, when the anterior roentgenogram is "negative."

(2) The earliest lesion clearly visible in the anterior roentgenogram in clinical tuberculosis is ordinarily in the subapical or in the infraclavicular region. For the most part, the apex above these acute lesions is clear; so much so, that it has been stated that "free apices occur almost exclusively in patients with sudden onset" (1). This appearance has led to the belief, in some quarters, that phthisis always has its origin in the subapical or infraclavicular region, and that when the apex is involved in progressive tuberculosis it has become so as a result of upward extension of the infection from the subapical region. Since the frequency of subapical infiltration is greater than can be accounted for by excessive exposure, this belief has necessitated the assumption that many of these infiltrations are merely allergic reactions of the lung tissue around slight, previously dormant tuberculous lesions (2), not visualized roentgenographically. However, if all cases of subapical infiltration are routinely X-rayed in the posterior lordotic position, the great majority of them will show small areas of fibrosis and emphysema in the apex (figures 5 and 6). In view of the greater frequency of subapical infiltration than can be accounted for by excessive exposure and the infrequency of isolated subapical autopsy scars, which is contrary to the assumption of dormant lesions in this region, the great frequency of older apical findings in association with subapical infiltration would appear to be strong roentgenological evidence negating the generalization that phthisis always has its origin in the subapical region. These findings, however, do not preclude the possibility that an associated subapical infiltration might be the result of a separate exogenous reinfection.

The roentgenological findings in the posterior lordotic position thus corroborate the pathological view that subapical and infraclavicular infiltrations may arise as a result of progression of, or aspiration of bacilli from, small apical lesions not recognizable in the routine roentgenogram of the chest. In this connection, the following statement by Rich (8) is worth noting: "... one must assume either that most lesions that appear roentgenographically to be limited to the infraclavicular region have their origin in an apical lesion not revealed by the x-ray, or else that, in most cases, lesions arising in the infraclavicular region spread upwards early in their course to involve the apex with roentgenographically invisible lesions." These "roentgenographically invisible" lesions may be made visible in the posterior lordotic view and the greater age of these lesions as compared with the subapical infiltration lends weight to the belief that most subapical infiltrations have their origin in an apical lesion.

(3) No direct evidence for the significance of these small fibrotic lesions in the production of clinical tuberculosis is available; some indirect evidence may, however, be adduced. A recent report (6) on tuberculosis in the Army indicates that the annual number of discharges for tuberculosis is 0.30 per 1,000 men under 20



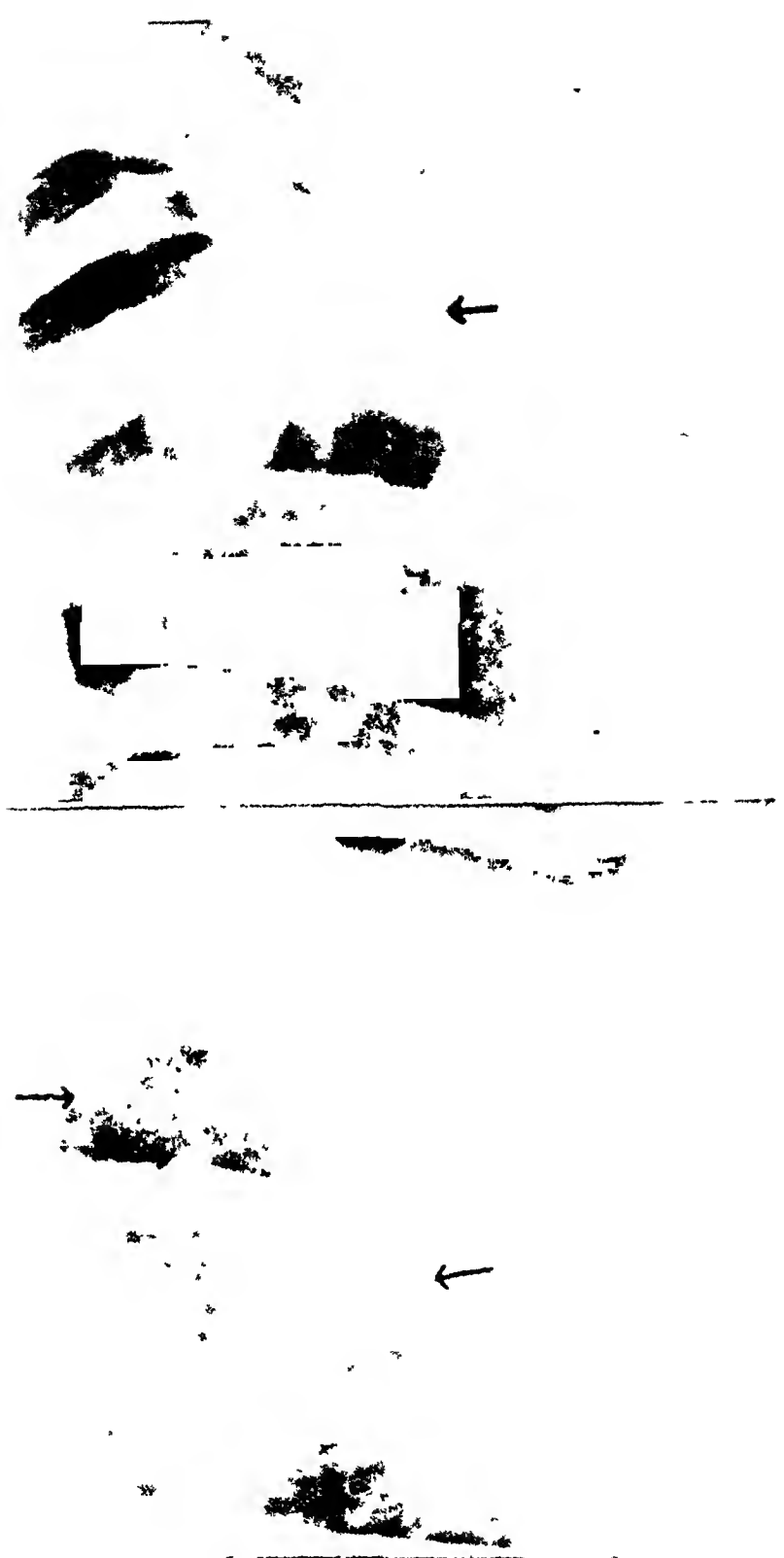


FIG 5 (Top) Routine anterior view. Arrow indicates an exudative infiltration.

FIG 6 (Bottom) Posterior lordotic view. Arrow on reader's right indicates the exudative infiltration seen in figure 5. The other arrows point to small areas of fibrosis and to "hollow forms."

and 2.56 per 1,000 men over 40 years of age, which provides a morbidity ratio of 8 to 1 for these age groups. This morbidity ratio appears to be in accord with current morbidity trends in the population at large in the United States for the same age and sex groups. This accord is rather surprising, inasmuch as the men in the Army form a select group whose members were X-rayed prior to induction. By way of explanation, a second report (7) states: "In the majority of cases of tuberculosis discovered in the Army, comparison with the induction film shows that a lesion was present on acceptance." The percentage of previously present tuberculosis thus found in each age group is not stated. It would be indeed strange if the errors in interpretation at induction stations were committed in the same ratio with regard to these age groups as their morbidity ratio. The present writer believes that, mathematically speaking, the morbidity ratio is a function of the small apical fibrotic areas revealed by the posterior lordotic projection.

This belief is based on the comparison of 100 "essentially negative" films of men past 35 with an equal number of "negative" films of an 18 to 20 year group, all these men being examined at an induction station. The only noteworthy difference between these two groups of films was the much greater frequency—about 6 to 1—and the greater extent of small apical fibrotic areas and emphysema in the older age group, as visualized in the posterior lordotic projection. It is believed that the ratio of these findings in otherwise "negative" films parallels too closely the morbidity ratio to be mere coincidence, especially in view of the fact that the predominant type of pulmonary tuberculosis in the Army is of the chronic ulcerative form. In consequence of the greater frequency and extent of apical fibrotic areas in the older age group, there is a far greater chance that some of these areas may harbor viable tubercle bacilli. The morbidity ratio for these two age groups is thus, in part, understandable.

#### SUMMARY

1. A modified posterior lordotic projection is advocated for the detection of early latent apical tuberculosis.
2. The application of these early findings to some problems in the pathogenesis of tuberculosis is discussed.

#### SUMARIO

1. Para el descubrimiento de la tuberculosis apical latente temprana recomiéndase una proyección lordótica posterior modificada.
2. Se discute la aplicación de estos hallazgos tempranos a ciertos problemas de la patogenia de la tuberculosis.

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## EMPLOYMENT OF EX-TUBERCULOUS PATIENTS<sup>1</sup>

H. S. WILLIS

The attack on tuberculosis has yielded some unrealized sources of personnel for hospital use, but such sources have been overlooked in general. Patients have recovered from their tuberculosis only too often to languish at home for months or years because suitable employment cannot be had or—more likely—because the public shies away from hiring the ex-tuberculous patient through fear of contracting his disease. When patients are treated, discharged and declared able to work, they are usually employable at a number of occupations. One occupation in particular makes an appeal to many such patients because, in general, it is not too strenuous and is relatively sheltered. This is employment in hospitals or sanatoria. Employment of ex-tuberculous persons by hospitals and sanatoria is not utilized nearly to the extent that would be highly profitable to such institutions. Although sanatoria have used their own graduate patients to some extent, hospital administrators seem to have had a particular blind spot in respect to this source of available manpower. Now, even at war's end, scarcity of help is a steady headache for hospital administrators everywhere. And at this time a fairly large pool of available help may be tapped if one seeks out the one-time tuberculous patient.

In common with the practice in many similar institutions, the Maybury Sanatorium has employed occasional ex-tuberculous patients in different categories of work. This experience, now about to be related, has been altogether such an agreeable one that it may profitably be expanded. The Sanatorium has 845 beds and 561 employees—or had that many places on its payroll before the war. Until recently this employee list was remarkably stable with extremely little turnover. Eighty-eight of its employees had had tuberculosis prior to employment. This is a very small proportion of the total employees over the years, but analysis of their employment record will interest any one charged with the duty of obtaining personnel. The 88 people involved represented a wide range of work—professional and nonprofessional. Among them there were physicians, nurses, clerical workers, attendants, orderlies, laundry workers, plumbers, messengers and others. Altogether these 88 people worked 559 man-years up to last July 1. And collectively they lost ten man-years of work from tuberculosis.

But one thinks of such former patients as being frail and delicate—as people to be placed only in certain chosen, so-called “easy” jobs—or people who would be absent from work for a multitude of other ailments than tuberculosis. What does the record show on this point? Unfortunately for the circumstances, accurate records for short-time losses were not kept prior to 1938. Details are available, however, on the absentee experience of 58 of these people as shown in table 1. Data collected on these 58 people covered 152 man-years of work or

<sup>1</sup> From Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

an average of 2.6 years each. They showed a total loss of 1,527 days' work from causes other than tuberculosis or practically ten days per person per year.

To obtain a control on time lost by nontuberculous employees, records of every fifth employee (active or resigned within the last three years) were tabulated if that person had worked one year or longer. The result, shown also in table 1, indicates that 100 nontuberculous employees, working 245 man-years or 2.45 years each, lost 2,300 days of work from causes other than tuberculosis. Thus an average loss of 9.4 days per year by this group stands in comparison to a loss of ten days per year by the ex-patient group. For practical purposes, therefore, the two groups lost essentially the same amount of time per year.

It is not possible to analyze the entire former employee personnel because records do not indicate the total number of employees or the number of years worked. Yet the records do show that altogether 26 employees who had no sign of tuberculosis upon taking their job developed the disease while at work and had 30 years of hospitalization or enforced inactivity therefrom. Thus three times as much absenteeism was experienced by 26 people who contracted tuberculosis while at work as was lost by the 88 employed ex-patients. These

TABLE 1

*Days lost per year by ex-patient employees and able-bodied employees: loss from illness other than tuberculosis*

	NUMBER OF EMPLOYEES	MAN-YEARS WORKED	AVERAGE NUM- BER OF YEARS WORKED	TOTAL DAYS LOST	DAYS LOST PER YEAR PER PERSON
Ex-patients.....	88	152	2.6	1,527	10
Able-bodied people.....	100	245	2.45	2,300	9.4

ratios are thought of as being only suggestive, because the numbers of able-bodied employees who did not develop tuberculosis are unknown but large.

How stable and how permanent are ex-tuberculous employees? The record here speaks for itself also. Of the 88, 40 are still employed in the Sanatorium, 41 resigned for reasons other than health, 2 left while in ill health from tuberculosis (one subsequently recovered and the other died), one died from tuberculosis and 4 died from other diseases (2 from carcinoma, one from cardiac disease, one from perforated peptic ulcer). This group of ex-patients has proved to be more stable than the average, with definitely less turnover. A good number of those who resigned did so to accept positions elsewhere in order to capitalize upon the experience they had gained at Maybury Sanatorium; some were attracted by the high wages of local war-busy industry.

The stability of these workers has proved the contention advanced by the United States Civil Service Commission (1) in respect to handicapped people in general. This Commission recently stated that, for such groups, the absentee record and the tardiness and turnover records are distinctly more favorable than those of able-bodied people. Upon emphasizing these contentions, the Associ-

ation of Casualty and Surety Executives (2) has indicated that handicapped employees "have fewer accidents (and) are conscientious, superior workers (who) expect no favors and produce as well as or better than the average of normal people."

Upon seeking employment, people who have had tuberculosis encounter serious rebuffs. They meet the indifference, prejudice and fear of industry and business. They learn that they are feared and shunned by many and are often treated like Pariahs. When some one hires them they very often are so appreciative of the opportunity to work remuneratively and thus, possibly, to reestablish themselves that they put forth every effort to make good. Such help will contain a larger than average proportion of loyal and eager workers.

But it may be asked whether a hospital assumes an added workmen's compensation liability by hiring such people in states where this disease is a compensable one. The answer appears to be this: if the ex-patient has met a set of rigid requirements before he is employed, his risk of "breakdown" appears to be small.

What criterion should be used as a measure of safe employability? This is the nub of the whole issue and is of telling significance. It would vary somewhat depending on the type of work and on the patient's previous experience with tuberculosis, especially whether he has had occasional exacerbations over a period of years. In general, a patient who has "handled" his tuberculosis well enough to leave the Sanatorium as arrested has a reasonably good prospect of continued health. Such a person should go through the hardening process of moderate exercise at home under good medical supervision for three months or longer during which he gradually expands his exercise beyond the privileges he was allowed before discharge. If all has gone well—as physical, X-ray and laboratory review would reveal—he should be able to undertake employment, preferably half-time for another three months. The patient who has remained well through this rehabilitation scheme will very likely be quite a satisfactory risk.

Every state has a large reservoir of such good-risk people who could be reckoned as suitable for average hospital work. Their availability and their eagerness for employment and the conscientiousness which the average ex-patient would put into his new job—all these stand as valid recommendations for him, as does also the experience of institutions which have hired his kind. In a true sense, employment of such people amounts to a real opportunity for and responsibility of the hospital in the tuberculosis issue.

#### SUMMARY

1. Ex-tuberculous patients in all classifications have been employed to do sanatorium work.
2. Eighty-eight such people worked 559 man-years and collectively lost only ten man-years of work from tuberculosis.
3. Data for able-bodied employees on this point are not comparable, although

over the years 26 employees developed tuberculosis and experienced thirty years of hospitalization therefrom.

4. On the average the ex-tuberculous patient loses no more time from non-tuberculous illness than the so-called able-bodied employee.

5. Ex-tuberculous patients work loyally and well—they know from experience that jobs are not easily obtained because of a well-established fear and prejudice. When they obtain employment, therefore, they tend to do creditable work.

#### SUMARIO

1. En los trabajos de sanatorio se han empleado ex-tuberculosos de todas clases.

2. Ochenta y ocho de estas personas trabajaron 559 años-hombre y colectivamente sólo perdieron diez años-hombre a causa de la tuberculosis.

3. No se puede comparar esta información con la relativa a empleados sanos, aunque a través de los años 26 empleados mostraron tuberculosis que ocasionó 30 años de hospitalización.

4. En conjunto, los ex-tuberculosos no pierden más tiempo debido a enfermedades no-tuberculosas que los llamados empleados capaces.

5. Los ex-tuberculosos trabajan bien y lealmente, habiéndoles enseñado la experiencia que no les es fácil obtener empleo a causa del arraigado temor y prejuicio, por lo cual, al obtener empleo, tratan de realizar buen trabajo.

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# PATIENTS' INFORMATION ABOUT TUBERCULOSIS<sup>1</sup>

A Survey with a Standardized Questionnaire

JOSEPH NEWMAN<sup>2</sup>

Education has played a most significant rôle in the fight against tuberculosis. Parran (1) has stated that "(Tuberculosis control) was the first instance in which we undertook to control a disease, not by specific immunization or quarantine, but essentially by the power of public education." Thus, education properly occupies a conspicuous position in the activities of antituberculosis organizations and its main emphasis has been directed toward the general public. In the light of the extensiveness of this education, it is surprising indeed to find that educational programs for tuberculous patients have been few and relatively novel, once we pass beyond the media of printed materials.

There is little doubt that the importance of increasing patients' knowledge and understanding about tuberculosis, and its implications as a disease, is gaining wider recognition among workers in the field. This is an expected development since tuberculosis control, both in relation to the individual and to society, revolves around the care that is exercised by patients. In a large measure, keeping the gains made while in a hospital, sanatorium or through any other means of curing depends upon the individual's understanding and sense of responsibility. As a social disease which can only be spread through existing cases, control of further spread can be made only at the source—the infected individual. This last fact alone makes it imperative that every possible means be undertaken to raise the level of knowledge and understanding about tuberculosis for each patient.

Such education, to reach its highest degree of effectiveness, should be an individual matter since there will be differences among patients as to intelligence, background and personality factors, such as receptiveness, emotional stability and sense of responsibility. These factors would affect any educational procedure. It seems logical that each individual patient should be appraised in these respects as the starting point in this education. As part of this appraisal, the question of how much the individual already knows or does not know and understands or misunderstands quickly arises. In which direction shall the educational efforts be concentrated? As a means to achieve this goal efficiently and reliably, the author undertook to devise a standardized questionnaire of tuberculosis information.

## DEVISING THE QUESTIONNAIRE

The use of standardized questionnaires or tests is an accepted procedure in educational practice, and, naturally, these have found their greatest application in scholastic use. However, the adaptation of methods so successfully developed

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in the general scholastic field to patient education has not been wide-spread. In the past, several questionnaires have been developed and used exclusively for survey purposes with various segments of the general population. These questionnaires were drawn up to discover the extent of information about tuberculosis along certain preconceived lines.

The present questionnaire devised by the writer represents an effort to utilize standardized testing techniques in the education of patients. It was made up by literally going through hundreds of leaflets, pamphlets, books, periodicals and patients' publications in order to select those facts on tuberculosis that have general acceptance as being essential in patients' knowledge. One hundred questions were drawn up from these items, and these formed the tentative questionnaire. The questionnaire was then administered to 195 patients; 84 "new" patients<sup>3</sup> and 111 "old" patients who had been in the institution for some time. The median age was 23 years and the range from 15 years to 55 years. There were slightly more than twice the number of men than women.

The questionnaire was also submitted to a group of 50 workers in the tuberculosis field which included physicians, nurses, occupational therapists, research workers and rehabilitation workers, and as a group constituted the "experts." The purpose of this group was to determine validity, correct answers and ambiguity. When 90 per cent or more of this group answered an item in any given way this answer was taken as the correct one; anything less was considered "ambiguous."

The final questionnaire was made up from those items which showed the ability to discriminate in so far as tuberculosis knowledge is concerned between a well-informed group and any other group; this discriminating value was determined by the critical ratio method and was calculated for each item between the expert and patient group, and between the new and old patients. There remained a group of 40 items which showed significant critical ratios between the above groups, and these comprised the final questionnaire.

The tentative questionnaire was also administered to a group of 178 summer session students in one of the New York City Colleges,<sup>4</sup> ranging in age from 16 to 38 years with the median at 20 years. The group was divided approximately equally into males and females. These students represented a highly selected portion of the general population, and may be considered as superior intellectually.

As rough indicators of trends, it was assumed that when there was correspondence in the answers of the college students with those of the new patients, who are largely those whose illness is newly discovered, this was a fairly reliable sign of a trend of thinking and certainly one to be investigated further. Added

<sup>3</sup> For the proper interpretation of the results it should be kept in mind that the new patients may have had some prior education in tuberculosis from the public health nurse before admission or else were patients in other institutions.

<sup>4</sup> The author gratefully acknowledges the kindness of Dr. J. G. Peatman of The City College of New York in obtaining the coöperation of the various student groups and for making many valuable suggestions.

evidence of the prevalence or persistence of the information trend could be obtained through comparison with the answers of the old patients. This comparison would also indicate the effectiveness of the sanatorium or hospital education in indicating misconceptions and strengthening correct ideas. An analysis of the answers of the various test groups to the tentative questionnaire is now presented.

### RESULTS

Comparison of results with surveys made in the past can only be made in the most general way chiefly because of differences in wording of questions. Workers in the field of public opinion surveys recognize the influence of the wording of a statement upon the answers obtained. In addition, there is the fact that different population samples were used.

(a) *Nature and causes of tuberculosis:* Past surveys have showed that there is a very wide belief that tuberculosis is inherited: from 46 (2) to 53 (3) per cent of the group responding to a true-false question. Gallup, whose survey (3) showed 53 per cent, had a somewhat contradictory result when, in response to a question asking the cause of tuberculosis, only 11 per cent gave "bad heredity" as the cause. The other answers dealt with infection, poor living conditions and poor health. One author has suggested the possibility that the public is somewhat confused on the term inheritance and even communicability. The result of 11 per cent indicating inheritance specifically as the cause is closely approximated by a Tulsa (Oklahoma) survey (4) which found 8 per cent stating inheritance. The World's Fair Survey (8) found 47 to 45 per cent believing tuberculosis may be inherited.

In the present questionnaire, one item dealt with causes specifically:

	<i>New Patients</i>	<i>Old Patients</i>	<i>College Students</i>	<i>Experts</i>
You get tuberculosis				
by being born with it;	7%	2%	1%	0
from someone who has it;	57%	90%	61%	100%
by having weak lungs;	21%	6%	32%	0
because you can't prevent it.	12%	2%	3%	0

"By being born with it" deals most directly with inheritance. This seems to be fairly well understood. The answer "by having weak lungs" may have some elements of thinking in terms of inheritance but it also has elements of thinking in terms of communicability and infection.

It seems safe to assume that these groups understand the infectious nature of tuberculosis. There is, however, a fairly large proportion that thinks in terms of constitutional deficiency perhaps as a result of inheritance or perhaps as the basis for contagion.

Added evidence of the general understanding as to the contagiousness of tuberculosis is found in the answers to other items: 90 per cent and over of all groups thought it is possible to prevent the spread of tuberculosis; 87 per cent and over of all groups thought it necessary to X-ray all members of the family when tuberculosis is found in the family.

Negative answers to the statement, "It is possible for tuberculosis germs to remain alive outside the human body for weeks and still be able to cause tuberculosis," were 23 per cent for new patients, 11 per cent for old patients, 24 per cent for college students and 8 per cent for experts.

Affirmative answers to "The closer the contact you've had with a tuberculous patient the greater the chance to get tuberculosis" were 82 per cent for new patients, 81 per cent for old patients, 76 per cent for college students and 94 per cent for experts. These same groups responded affirmatively to "An arrested case of tuberculosis may be a safer companion than a person who has never been examined for tuberculosis" as follows: 82 per cent, 91 per cent, 77 per cent and 96 per cent.

Most of the answers, 66 per cent and over, indicate understanding that tuberculosis may occur at any age; the answers for the experts were 90 per cent. About 20 to 27 per cent believe it is mainly a disease of young adults; 77 per cent of the old patient group believe tuberculosis may occur at any age and 15 per cent believe it is mainly a disease of young adults.

Summing up these findings, it appears to be quite well established in our society's beliefs that tuberculosis is not inherited and is not a fatal disease. Less well established is the understanding that an infection of a contagious nature is the cause of tuberculosis. There are, however, sizable groups whose knowledge is deficient as to the exact contagious nature of tuberculosis. There is some evidence of thinking in terms of constitutional deficiency.

(b) *Hygienic measures that should be observed:* In the light of the findings in the previous section, it is interesting to survey the results on the statements dealing with hygienic measures to be practiced by patients with tuberculosis. All groups recognized that strict personal cleanliness is especially important for the tuberculous patient. The affirmative answers were all 93 per cent or over. Even higher percentages recognized the necessity for using sputum cups and paper tissues as hygienic measures. However, the disposal of these seemed to be the source of some misunderstanding; 44 per cent of the entire patient group thought "It is not necessary to burn sputum cups and paper tissues;" the college group answers were 12 per cent in this direction, and 4 per cent of the experts agreed. These answers were checked by the statement, "The best way to kill possible tuberculosis germs are by boiling and burning." The negative answers were 15 per cent for new patients, 10 per cent for old patients, 55 per cent for college students, and 9 per cent for the experts.

The necessity for having separate linen, silver, dishes and other articles and that these may be a source of infection seem to be well understood in 90 per cent and over in all groups. On the other hand, the affirmative answers to the statement, "When you are at home, the only necessary precaution is that you have your own room," are 28 per cent for the new patients, 22 per cent among old patients, 7 per cent among college students, and 2 per cent for the experts. These percentages suggest some misunderstanding especially among the patient groups. This contradiction seems to indicate a lack of real understanding or, rather, a

lack of certainty of understanding since differently worded statements can evoke different trends in answers. The understanding that general hygienic living and avoidance of contact with open cases are important was found to be shared in 91 per cent of the group reported by Kilander. These findings largely corresponded to the results of the present questionnaire in this area.

(c) *Diagnosis and treatment:* There were 3 items dealing with symptoms. In response to the statement, "Early tuberculosis may have no symptoms," negative answers ranged from 18 per cent in the old patient group to 22 per cent among the college students and 7 per cent among the experts. In response to the statement, "Symptoms appear more often with advanced tuberculosis," the negative answers of the patient groups are about the same, 19 and 20 per cent. However, the college group has only 6 per cent negative answers (the experts have 8 per cent negative answers). The explanation for this may be that one may logically expect symptoms with advanced tuberculosis and, hence, we may expect a superior group to do well on this statement. However, the same does not hold for knowledge of the symptomatology in early tuberculosis. These approximately 20 per cent of these population samples misunderstand that early tuberculosis may be without symptoms although they more often will recognize that advanced tuberculosis has symptoms.

The question arises as to what these groups do recognize as symptoms. They were asked to select the three most common symptoms from a list of eight. The results are as follows:

	New Patients	Old Patients	College	Expert
Loss of weight . . . . .	75%	75%	72%	70%
Cough . . . . .	48%	49%	72%	50%
Tiredness . . . . .	69%	55%	57%	70%
Spitting blood . . . . .	63%	65%	62%	70%
Loss of appetite . . . . .	49%	48%	27%	70%
Nervousness . . . . .	5%	5%	12%	0%
Paleness . . . . .	4.5%	7%	0%	0%
Sleeplessness . . . . .	4.5%	7%	0%	0%

The symptom that had the highest percentage of selection in all groups, although never higher than 75 per cent in any group, except for the experts, is "loss of weight." The second highest for the patient groups is "spitting blood;" this occupies third place in the selection of the college group. Second in the college group is "cough;" this occupies fourth and fifth place in the patient groups. "Tiredness" is the third choice of the patient groups and second of the college group. The opinions of the experts are "loss of appetite," "paleness" and "cough;" the same three come close to the top of the list for the expert group, with the exception that "sleeplessness" is placed third in the list. These results indicate that, while there is fairly good knowledge of the symptoms of advancing tuberculosis, there is still a marked lack of knowledge of the dramatic signs such as hemoptysis and paleness. From the point of view of the health point of view it would have been desirable to have more emphasis on

were recognized, such as tiredness and loss of appetite; these were selected in only 33 per cent and 27 per cent of the choices as against choices from 66 per cent to 72 per cent for the three highest.

The tendency to rely upon traditional symptoms in thinking about tuberculosis is further emphasized by the negative answers to the statement, "Successful athletes have been found to have tuberculosis;" 11 per cent of the new patients, 9 per cent of the old patients and 25 per cent of the college group did not believe so.

While certain symptoms are associated with tuberculosis, it is gratifying to note that there is a reliance upon scientific means of diagnosis to determine the presence of tuberculosis. This conclusion is substantiated by the answers to the statement: "The best way to diagnose tuberculosis is"

	<i>New Patients</i>	<i>Old Patients</i>	<i>College Students</i>	<i>Experts Subgroup Physicians</i>	
By X-ray .....	79%	80%	63%	40%	} 60% suggested combination of methods
Sputum examination .....	12%	11%	7%	0	
Tuberculin test .....	8%	9%	30%	0	
Physical appearance .....	1%	0	0	0	

The most significant finding in these figures is the low percentage of the answers for physical appearance. "Physical appearance" is not identical in eliciting answers as selecting symptoms. Thus the very low percentages choosing "physical appearance" do not show any contradictions in answers as compared with those dealing with symptoms. For the college group the word "tuberculin" in tuberculin test may have been suggestive. In view of this group's general sophistication as to examination-taking, this fact may not have been completely influential in determining the answer. Most satisfactory is the apparent understanding that there should be reliance upon scientific means of diagnosis. Ideally we should have wanted to see a greater percentage selecting X-ray. The World's Fair Survey found that 73 to 75 per cent recognized X-rays as a diagnostic aid in the early stages of tuberculosis.

Information about modern methods for treating tuberculosis were tapped by many questions. The various groups were asked to select the three most important parts of good treatment from a list of eight. The choices are listed.

	<i>New Patients</i>	<i>Old Patients</i>	<i>College Students</i>	<i>Experts</i>
Rest .....	93%	99%	93%	98%
Good food .....	75%	90%	63%	96%
Cheerful attitude .....	36%	42%	27%	54%
Fresh air .....	72%	54%	69%	42%
Medicine .....	6%	0	12%	9%
Mountain climate .....	9%	6%	18%	0
Outdoor life .....	3%	0	3%	0
Special diet .....	6%	9%	15%	0

The most evident fact is the recognition of rest as an important component of treatment. However, there seems to be some doubt that it is the most important

component. One question dealt with this specifically: "The most important treatment of tuberculosis is"

	<i>New Patients</i>	<i>Old Patients</i>	<i>College Students</i>	<i>Experts</i>
Food.....	9%	13%	1%	0
Medicine.....	0	0	2%	0
Fresh air.....	13%	10%	31%	0
Rest .....	78%	77%	66%	100%

Among the patient groups 22 to 23 per cent chose other parts of treatment—food and fresh air—as more important than rest. In the college group, 34 per cent chose other aspects of treatment as more important than rest; 31 per cent choosing fresh air.

The findings of other surveys tend to be contradictory. The questions were similar to the above where the respondents were asked to select the most important item in the treatment of tuberculosis. Gallup found 43 per cent of his group selected rest. Pollok (5) found that in her group two-thirds chose "going to a dry climate" as the treatment. Kilander reported that about 90 per cent of his groups stated that rest, rather than medicine or diet, is the most important single procedure in the treatment of tuberculosis. Kilander's results may be explained by the choices presented, of which climate was not one. The World's Fair Survey found that 89 to 92 per cent of the groups tested thought rest is the most important single item in treatment of tuberculosis. This survey found a somewhat contradictory result as to climate; 50 to 52 per cent thought a dry, warm climate is not essential, whereas, when the same question was worded positively, the percentages who answered negatively were 67 to 82. Thus, while the present questionnaire indicates that rest is regarded as an important component of good treatment more often than any other component, there is a considerable group that does not regard it as the most important component.

The relation of rest to other phases of treatment is tapped by the statement, "If rest is the chief treatment, then the cure can be taken at home." Substantial percentages answered this statement in the affirmative: 31 per cent of the entire patient group and 26 per cent of the college group. This seems to indicate a tendency not to consider the importance of close medical supervision. This is particularly true of the patient groups who, in response to the statement, "If you rest you don't need medical attention," agreed in 30 per cent of the answers. The college group, however, fully recognized the need for medical attention even if rest is observed.

Among the three important components of treatment, "good food" occupies second place. The exact significance of diet is explored by the statement, "It is of value to be overweight." The affirmative answers are 27 per cent for new patients, 12 per cent for old patients and 11 per cent for college students. Thus, while proper diet was properly recognized as significant, there is a residue of misunderstanding of the relationship of weight as a health factor.

Gallup found that 36 per cent thought diet was the best way to cure tuberculosis. Kilander found that 7 per cent thought diet more important than rest and medicine. Kilander's choices limit somewhat the value of his information in this respect. Gallup's findings are close to those of this study.

In considering the most common third choice for proper treatment, "fresh air," it might be well to analyze the answers revolving about climate. Obviously "fresh air" is not the same as "climate" as a choice in good treatment. Thus the answers to the statement, "Climate is the most important part of the treatment," would not be of the same significance. There are several possible interpretations of "climate" but the most probable seems to be in terms of an Arizona-dryness and mountain altitude. Some clue can be obtained from the analysis of the choices for the three important parts of the treatment. "Fresh air," "mountain climate" and "outdoor life" are related and, of these, "fresh air" shows the greatest percentage of choice. Much lower are "mountain climate" and "outdoor life."

When the affirmative answers to the statement, "You should stay out in the sun as much as possible," (25 per cent for new patients, 13 per cent for old patients, 74 per cent for college students and 10 per cent for the experts) are considered along with the answers to the statement on climate above (32 per cent for new patients, 14 per cent for old patients and 36 per cent for college students) we can see a trend in thinking along the traditional lines of treating tuberculosis. Also the affirmative answers to the statement, "Outdoor work is best for the arrested case," (71 per cent for new patients, 35 per cent for old patients, 89 per cent for college students and 10 per cent for experts) underline this trend. There appears to be wide misunderstanding as to climatic factors in treatment and maintaining health, particularly as to being outdoors and as to sunshine. The World's Fair Survey found that health workers misunderstood the effects of climate on tuberculosis.

The expert groups ranked "cheerful attitude" in third place. This was the finding for the physicians subgroup. "Cheerful attitude" takes on increasing weight as a factor among patients, comparing the new patients with the old patients. For the patient and professional groups, the importance of emotional factors assumes greater and greater significance. In a series of statements on mental attitude and peace of mind, all groups indicated their importance in 90 per cent and over of the answers.

The wide scatter of answers in the college group regarding treatment suggests misunderstanding as to modern methods of treating tuberculosis.

From 24 to 29 per cent of the patient groups (the higher percentage is for the old patients) believe the free use of tobacco and alcohol makes little difference to their tuberculosis, whereas only 10 per cent of the college group think so and 4 per cent of the expert group.

Understanding as to the value of early diagnosis is revealed to some extent by the answers to the statement, "Since treatment in tuberculosis takes so long, delay in treatment makes little difference." The only significant percentages of answers in the affirmative came in the patient groups; 19 per cent of the new patients and 27 per cent of the old patients. The affirmative answers from the

expert and college groups were 4 and 1 per cent, respectively. The greater percentages among the older patients are possibly the result of a fatalistic or pessimistic outlook as the result of long hospitalization.

There seems to be a surprisingly wide-spread misunderstanding as to the erratic and medically eventful course of tuberculosis as an illness as judged by the answers to the statement, "Treatment in tuberculosis is slow but it runs smoothly." The percentages of affirmative answers run 71 for new patients, 60 for old patients and 62 for college students. The fact that this misconception is strongest among new patients and quite high among college students indicated that it has nothing to do with the type of case in Otisville.

There seems to be recognition of the fact that each case of tuberculosis has to be judged by itself in view of the affirmative answers to the statement, "Each case of tuberculosis is different." The patient group answers were over 90 per cent. However, among the college students the affirmative answers were 69 per cent.

The value of subjective feelings as measures of medical progress is tapped by two statements, although not precisely in the first of these. The affirmative answers to "If you feel all right, you are all right" are 11 per cent and 7 per cent for the new patients and the old patients, respectively. Almost all the college students answered this negatively. On the other hand, the affirmative answers to "The best way to judge how you are getting along is how you feel" were 30 per cent for the new patients, and 5 per cent for the old patients and 18 per cent for college students. This statement deals more directly with illness whereas the previous statement, while intended to be judged in relation to tuberculosis, does not state the illness explicitly and may have been judged as a general statement, not particularly related to tuberculosis. The results indicate a fairly large misunderstanding upon admission as to judging one's condition according to subjective feelings.

The significance of a negative sputum in relation to the nature of the tuberculosis process seems to be a point around which there is some misunderstanding. The affirmative answers to "Negative sputum means no tuberculous activity" are 45 per cent for new patients, 38 per cent for old patients, and 48 per cent among college students.

Coughing is believed to be of diagnostic value among 14 per cent of the new patients and 11 per cent of old patients. Fewer, 3 per cent and 7 per cent for these groups, believe it to be of no value. Fifty per cent of the new patients and 36 per cent of the old patients believe coughing is harmful. That coughing "is of value only when it brings up sputum" is believed by 33 per cent and 45 per cent of these groups; this is the choice of 80 per cent of the physicians subgroup. The scatter of answers among the college group is much wider.

The answers to this last group of statements seem to indicate that among new patients in particular is there unduly prevalent misunderstanding as to some specific facts about tuberculosis as a disease which is affecting them. Particularly the uneven course curing might take and the significance of sputum are areas in which there is deficiency in knowledge.

Patients seem to recognize that knowledge about tuberculosis is important



for them. They recognize also that the doctors are the ones with whom they should discuss their condition.

Understanding of the inadvisability of leaving before a proper medical discharge was explored with two statements, "Once you become ambulatory and the illness inactive, it is all right to go home without a discharge," and "A patient who leaves against advice has just as good a chance to get well and keep well as the patient who stays until discharged." The negative answers for both these statements were over 90 per cent for all groups.

The necessity for adequate sleep each night seems well recognized. However, substantial percentages, 25 to 38 per cent, believe in sleeping "as much as you can."

(d) *Care after discharge:* Care after discharge is also well recognized both as to the necessity for following rules learned while in the sanatorium and as to regular and routine check-up after discharge. The overwhelming majority recognize that the period after discharge is "dangerous." Substantial percentages among the patients, 25 and 31 per cent, believe this "dangerous" period extends throughout life. The necessity for caution seems well recognized.

In general, the patient groups have a pessimistic outlook as to the future. Substantial proportions believe that little can be done to help the discharged patient (29 to 39 per cent), that they can't get married (25 to 28 per cent) and that a normal life is out of the question (31 to 33 per cent). This seems to be related to the fatalistic thinking that is common, and a fear of the chronicity of tuberculosis.

There is a general recognition of the value of sanatorium care and its advisability: 90 per cent of all groups recognize the sanatorium as the best place for treatment. However, patients on admission tend to think in terms of time limits upon their length of stay. While most recognize that, in general, it is easier to have mental ease in the sanatorium, a fairly large group (14 to 19 per cent) believe peace of mind is easily achieved at home. In this connection, new patients more often want many and frequent visitors: 26 per cent as against 14 per cent for old patients.

There is a rather general disinclination to make plans for future work while a patient, especially among new patients. The percentage is 70 as against 39 per cent for the old patients. The same outlook exists among college students as among the new patients.

#### SUMMARY

The results of the questionnaire findings show that the following points about tuberculosis are generally understood in the various groups sampled (exclusive of the professional tuberculosis workers):

- 1: Contagiousness is a factor to be considered in tuberculosis.
- 2: Tuberculosis is not inherited.
- 3: Tuberculosis is not fatal.
- 4: Rest is an important part of treatment.

- 5: Mental factors are significant in treatment. (A trend towards pessimism and fatalism was found among the patient groups.)
- 6: Each case of tuberculosis is different.
- 7: Coughing has no diagnostic value.
- 8: It is important to have knowledge about tuberculosis as a disease.
- 9: The best source of information about one's condition is the doctor.
- 10: Recognition of the value of sanatorium care.
- 11: The advisability of waiting for a proper medical discharge before leaving the sanatorium.
- 12: The necessity for follow-up care after discharge.
- 13: The advisability of sufficient sleep each night.
- 14: The necessity for hygienic measures in the home.

The following points showed improvement in understanding, comparing the old patients with the new patients:

- 1: The specific means of acquiring tuberculosis.
- 2: The viability of tuberculosis germs.
- 3: Being overweight is of no value.
- 4: Outdoor work is not advisable.
- 5: Unlimited exposure to the sun is not advisable.
- 6: Frequent and numerous visitors are not advisable.
- 7: The value of making plans for the future while a patient.
- 8: The inadvisability of judging one's progress by subjective feelings of good health.

The following points were understood to a lesser degree, the degree of misunderstanding ranging from one-fifth to one-third of the groups:

- 1: Nature of contact for contracting tuberculosis.
- 2: Isolation at home is not enough as a preventive measure.
- 3: Tuberculosis may occur at any age.
- 4: Rest is the most important part of treatment.
- 5: Inadvisability of delay in treatment.
- 6: Rest at home without medical attention is insufficient.
- 7: X-ray is the best diagnostic means.
- 8: The value of climatic factors in treatment.

The following points seemed to be generally misunderstood:

- 1: Tuberculosis as an illness may run an erratic course.
- 2: The necessity for radical measures to destroy used paper tissues, such as by burning.
- 3: Recognition of subtle symptoms of tuberculosis.
- 4: Association of dramatic and traditional symptoms with all tuberculosis.
- 5: The significance of negative sputum in relation to progress.

#### CONCLUSIONS

The results of the analysis of the answers of various groups indicate that there is no broad configuration of understanding or misunderstanding concerning tuberculosis and its treatment in the various groups sampled. Rather there is

considerable individual variation. The present questionnaire seems to offer itself as an effective means to explore and remedy such variation. This is necessary as a beginning step in the education of tuberculous patients.

#### CONCLUSIONES

Los resultados del análisis de las respuestas de varios grupos indican que no existe un patrón general de comprensión o incomprensión acerca de la tuberculosis y su tratamiento en los varios grupos estudiados, encontrándose más bien considerable variación individual. El presente cuestionario parece ofrecer un medio eficaz para explorar y remediar dicha variación lo cual resulta necesario como paso preliminar en la educación de los enfermos tuberculosos.

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# RESULTS OF PNEUMONOLYSIS<sup>1</sup>

HENRIETTE MARCUS AND MAX PINNER

To investigate the end result of treatment in patients who were subjected to pneumonolysis in the course of treatment for pulmonary tuberculosis, 302 consecutive cases were studied. The operations were performed at the Montefiore Hospital and the Montefiore Country Sanatorium between February, 1937 and June, 1943 by Doctors A. Aufses and I. Kross. Thirteen of the 302 patients had bilateral simultaneous pneumothorax and thoracoscopy was performed on each side, thus bringing the total pneumothoraces under consideration up to 315. In all, 302 patients were operated on 401 times.

Of the 302 patients, 80 were moderately advanced and 222 were far advanced. There were no minimal cases in this series.

Seventeen of the patients had tuberculous complications:

Tuberculosis of bone.....	1
Tuberculous bronchitis.....	7 (1 on the contralateral side)
Tuberculosis of larynx.....	4 (extensive only)
Tuberculosis of gastrointestinal tract.....	4
Tuberculosis of genitourinary tract.....	2

These complications were present at the time of operation. Many more were observed during the subsequent course of the patients, but these have no bearing on the subject under consideration and will, therefore, not be discussed.

The nontuberculous complications were as follows:

Diabetes.....	15
Arteriosclerotic cardiovascular disease.....	5
Rheumatic heart disease.....	3
Essential hypertension.....	2
Glomerulonephritis.....	1
Hyperthyroidism.....	1
Glaucoma.....	1
Peptic ulcer.....	2
Asthma.....	1
Sprue.....	1

To analyze the results properly, it is convenient to divide the pneumothoraces into four groups:

GROUP		NUMBER OF PNEUMOTHORACES	PER CENT
1	Complete pneumonolysis	88	28
2	Partial pneumonolysis	102	32
3	"Insignificant" pneumonolysis	24	8
4	Thoracoscopy only	101	32
	(a) No adhesions seen	3	1
	(b) No adhesions cuttable	98	31
Total.....		315	100

<sup>1</sup> From the Division of Pulmonary Diseases of the Montefiore Hospital for Chronic Diseases, New York, New York, and the Montefiore Country Sanatorium, Bedford Hills, New York.

Group 1 includes cases in which all adhesions were severed which were seen either preoperatively on X-ray films and fluoroscopy, or at the time of operation, and which were attached to diseased lung tissue. This includes the rare case in which adhesions were seen which held up portions of the lung other than the diseased area. Although such adhesions were not necessarily cut, these cases are still included in the "complete" group. Group 2 includes all cases in which key adhesions were cut completely or in part, but some adhesions, or parts of adhesions, remained intact. In group 3, some degree of pneumonolysis was performed, but the key adhesions were not cuttable. In this group one or more string adhesions were cut, which, at times, exposed the main body of the adhesions, and these were judged inoperable. In group 4a no adhesions were visible prior to operation and none were found at operation. Thoracoscopy was done because one patient remained positive in spite of apparently successful pneumothorax, one patient had persistently positive cultures and one patient had a small left lower lobe cavity which did not close, although he had no endobronchial lesion. In each case thoracoscopy was advised on the chance that adhesions might be present which could not be demonstrated roentgenographically or fluoroscopically. None of these patients suffered ill effects from the unnecessary procedure and all did well eventually.

## RESULTS OF OPERATION

*1: Favorable results directly attributable to operation*

GROUP	NUMBER OF PNEUMOTHORACES	IMMEDIATE CONVERSION (WITHIN 3 MONTHS)		LATE CONVERSION (3 MONTHS TO 1 YEAR)		APPARENTLY SUCCESSFUL, BUT REMAINED POSITIVE				TOTAL FAVORABLE RESULTS	
		Number	Per cent	Number	Per cent	Conversion after contralateral collapse therapy		Positive on account of contralateral disease		Number	Per cent
						Number	Per cent	Number	Per cent		
1	88	33	37.5	8	9.1	4	4.5	3	3.4	48	54.5
2	102	38	37.3	9	8.8	1	1.0	—	—	48	47.1
3	24	4	16.7	4	16.7	—	—	1	4.1	9	37.5
4	101	10	9.9	6	5.9	5	5.0	—	—	21	20.8
Total	315	85	27.0	27	8.6	10	3.2	4	1.2	126	40.0

*2: Favorable results not directly attributable to operation*

GROUP	NUMBER OF PNEUMOTHORACES	CONVERSION AFTER ADDITIONAL TREATMENT, SAME SIDE (OTHER THAN THORACOPLASTY)		NEGATIVE PREOPERATIVELY		CONVERSION AFTER DISCONTINUATION OF PNEUMOTHORAX (NO OTHER COLLAPSE THERAPY)		CONVERSION AFTER THORACOPLASTY		TOTAL FAVORABLE RESULTS	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
1	88	3	3.4	25	28.4	—	—	1	1.1	29	32.9
2	102	1	1.0	29	28.4	1	1.0	2	2.0	33	32.4
3	24	—	—	4	16.7	2	8.3	2	8.3	8	33.3
4	101	2	2.0	33	32.7	12	11.9	8	7.9	55	54.5
Total	315	6	1.9	91	28.9	15	4.8	13	4.1	125	39.7

*3: Total favorable results during hospitalization period*

	NUMBER	PER CENT
Results attributable to operation.....	126	40.0
Results not attributable to operation.....	125	39.7
Total good results.....	251	79.7

Total number of pneumothoraces considered—315.

*4: Unfavorable results*

GROUP	NUMBER OF PNEU- MOTHORACES	PROGRESSION		NO CONVERSION OR NO FOLLOW-UP		TOTAL UNFAVORABLE RESULTS	
		Number	Per cent	Number	Per cent	Number	Per cent
1	88	5	5.7	6	6.8	11	12.5
2	102	14*	13.7	7	6.9	21	20.6
3	24	5	20.8	2	8.3	7	29.1
4	101	21	20.8	4	4.0	25	24.8
Total.....	315	45	14.3	19	6.0	64	20.3

\* Two cases of tuberculous bronchitis.

## COMPLICATIONS

The complications of operations are expressed in terms of the type of operation performed. Therefore, the four categories are not quite identical with the original four groups.

*5: Postoperative fever*

	NUMBER	PER CENT
Less than 100°F.....	243	61
100°-101°F.....	86	21
101°-102°F.....	34	8
102° plus.....	38	10

Total number of operations considered—401.

*Effusions:* The commonest complication was the development of a clear effusion, often of very small extent and transitory in character. It was usually accompanied by slight to moderate temperature elevation, although high fever was seen in a few cases. The constitutional reaction was mild to moderate. It was not our practice to aspirate these effusions routinely for diagnostic purposes but only when special circumstances indicated the procedure. The incidence of clear transitory effusion, and the bacteriological findings in those aspirated, are listed in tabulations 6 and 7.

*6: Transitory effusions*

TYPE OF OPERATION	NUMBER OF OPERATIONS	NUMBER	PER CENT
Complete pneumonolysis.....	88	55	62.5
Partial pneumonolysis .....	142	79	56.7
Insignificant pneumonolysis.....	31	12	38.7
Thoracoscopy only.....	140	38	27.1
Total.....	401	184	45.9

*7: Bacteriological findings in transitory effusions*

TYPE OF OPERATION	NOT ASPIRATED	ASPIRATED— NEGATIVE SMEAR AND CULTURE	ASPIRATED— POSITIVE CULTURE	ASPIRATED— POSITIVE SMEAR	PER CENT POSITIVE OF THOSE ASPIRATED
Complete pneumonolysis.....	45	7	1	2	30
Partial pneumonolysis.....	60	12	5	2	37
Insignificant pneumonolysis.....	10	2	—	—	0
Thoracoscopy only.....	28	6	2	2	40

*Hemothorax:* Bloody effusions were seen 7 times. Six cases were mild and required no treatment other than aspiration of the effusion, either once or twice. No serious consequences were observed, although obliterative pleuritis made long continuation of pneumothorax impossible in 2 cases. Nevertheless, 6 of the 7 patients did well. One patient developed a serious intrapleural hemorrhage, and repeated transfusions and vitamin C and K therapy were needed to save his life. This man had been suffering from a chronic intestinal disorder for years, which had remained undiagnosed. Following pneumonolysis he not only developed intrapleural hemorrhage but also hematuria, epistaxis and purpura. On further work-up his intestinal condition was diagnosed as sprue. In his case hemothorax was also followed by obliteration within six months. He did well for two years, but later developed tuberculous pneumonia with spread into the other lung, and he has since shown hopeless progression. The distribution of the bleeding cases into the four types of operations is shown in tabulation 8. It is evident that there is no connection in our cases between the occurrence of bleeding and the extent of pneumonolysis.

*8: Bloody effusions*

TYPE OF OPERATION	NUMBER OF OPERATIONS	NUMBER	PER CENT
Complete pneumonolysis.....	88	1	1.1
Partial pneumonolysis .....	142	1	0.7
Insignificant pneumonolysis.....	31	3	9.7
Thoracoscopy only.....	140	2	1.4
Total.....	401	7	1.7

*9: Massive persistent effusions*

TYPE OF OPERATION	NUMBER OF OPERATIONS	NUMBER	PER CENT
Complete pneumonolysis.....	88	2	2.3
Partial pneumonolysis.....	142	8	5.6
Insignificant pneumonolysis.....	31	1	3.2
Thoracoscopy only.....	140	6	4.3
Total.....	401	17	4.2

*Massive persistent effusions:* Seventeen cases were observed (see tabulation 9). Three out of these 17 cases developed tuberculous empyema during the course of observation, all more than three months after the operation. The 3 cases have a distribution of one each in groups 1, 2 and 3. The onset of the empyema was not conspicuous. The fluid was aspirated for diagnostic purposes at regular intervals and was observed to become cloudy and eventually quite thick. Tuberculous empyema is, of course, a not uncommon complication of pneumothorax therapy, especially if pneumothorax is incomplete. It is, therefore, doubtful that these 3 empyemata should be charged to the operative procedure alone. Even in the case where complete pneumonolysis was performed it is unlikely that the empyema was the result of the operative intervention:

*Case 300:* A 35 year old male patient had a normal X-ray film in November, 1941 at a preemployment survey. He became acutely ill in April, 1942 with a caseous tuberculous pneumonia involving the entire left upper lobe. This excavated rapidly and pneumothorax was induced on April 28, 1942. He continued moderately febrile and developed fluid in May, 1942. The fluid was aspirated and was clear and negative for tubercle bacilli. Complete left pneumonolysis was done in June, 1942. It was followed by an increase in the effusion and a temperature rise of 103.2°F. Following this the patient made satisfactory clinical improvement, although his sputum did not become entirely negative. His temperature became normal and he gained weight. His pleural cavity was never free of fluid during his subsequent course. Bacteriological examinations were negative on smear and culture until December, 1942. In February, 1943 the first positive smear was obtained. The pleural cavity was aspirated and irrigated regularly from then on, while pneumothorax was maintained. In July, 1943 it was decided to reexpand his lung. This was not altogether possible and he had a three-stage thoracoplasty in February, March and April, 1945. He still has occasionally a positive sputum, and he still has a residual empyema cavity. However, it is felt that he has been benefited by the treatment, since pneumothorax seemed to have been a life-saving procedure for him. Development of tuberculous empyema is frequently seen when one is forced to give pneumothorax to a febrile patient with tuberculous pneumonia.

*10: Purulent effusions*

TYPE OF OPERATION	NUMBER OF OPERATIONS	TUBERCULOUS EMPYEMA		MIXED INFECTION EMPYEMA		STAPHYLOCOCCUS EMPYEMA (PURE)		TOTAL	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Complete pneumonolysis....	88	1	1.1	4	4.6	1	1.1	6	6.8
Partial pneumonolysis.....	142	5	3.5	4	2.8	—	—	9	6.3
Insignificant pneumonolysis..	31	—	—	—	—	—	—	—	—
Thoracoscopy only.....	140	1	0.7	—	—	—	—	1	0.7
Total.....	401	7	1.7	8	2.0	1	0.3	16	4.0



*Purulent effusions:* It is difficult to decide from a review of the patients' charts some years later whether or not the empyema had a causal relationship to the preceding operation. In the above table all empyemata which developed within the first three months following operation have been recorded but it is possible that this tabulation does not do justice to the procedure. Especially is that true of the pure tuberculous empyemata, because the development of purulent effusion is, at times, insidious and not accompanied by a systemic reaction. It is, therefore, difficult to place the onset of tuberculous empyema with any degree of accuracy. In one case no aspiration was done until six weeks postoperatively, because the patient's condition did not warrant it. When it was finally done aspiration revealed turbid fluid containing tubercle bacilli. Yet this patient developed thick pus within ten months of operation.

Another difficulty in the tabulation of tuberculous empyemata is the question of distinguishing between a very turbid fluid and thin pus. Two of the patients listed in the table never did develop thick pus. Their fluids, according to the laboratory reports, were described as "very cloudy" and "moderately turbid." Yet these patients were treated vigorously with aspiration, irrigation and attempts were made to reëxpand the lung.

Because of the pronounced systemic symptoms which usually accompany the onset of mixed infection empyema, it is much easier to date its onset, and there is no doubt that 7 out of the group of 8 so listed had a causal relationship to the operative procedure. In one case the causal relationship has not been definitely established. A small amount of fluid, accompanied by a low grade fever, developed immediately postoperatively in case 288. The temperature rapidly returned to normal, but the fluid did not entirely disappear. No diagnostic aspiration was done on this patient. Two months later he became acutely ill with the signs and symptoms which usually accompany a mixed infection empyema. Tubercle bacilli were then found in the fluid, and *Staphylococcus aureus* was found two weeks later. Within three months of the original operation this patient had thick pus in his chest. This patient, then, falls within the three months' limit, but it is doubtful whether his inclusion in the group is entirely justified. The one case of a pure staphylococcus empyema developed as a definite sequel to the operation.

The time relationship between the development of fluid, pus and the bacteriological findings is given in the following tabulations.

11: Tuberculous empyema

	STAT	0-1 MO.	1-2	2-3	3-4	4-5	5 PLUS	NEVER
First appearance of fluid.....	5	2						
First note of turbid fluid.....			3	1	1	2	•	
First note of thick pus.....			1	1	1		2	2
First demonstration of tubercle bacilli. . . . .		4	3					

*12: Mixed infection and pure secondary empyema*

	STAT	0-1 NO.	1-2	2-3	3-4	4-5	5 PLUS	NEVER
First appearance of fluid.....	8	1						
First note of turbid fluid.....		2	1					
First note of thick pus.....		6	2	1				
First demonstration of secondary organism.....	2	5	2					
First demonstration of tubercle bacilli.....		4	3				1	1

The onset of tuberculous empyema is usually accompanied by mild to moderate constitutional symptoms and moderately elevated temperature. One of the 7 patients never showed more than a low grade fever, not reaching 100°F. One patient had an elevation of less than 101°F., 3 patients fell into the 101 to 102 range and only one patient had more than 102°F.

Temperatures in excess of 102°F. generally accompanied the onset of mixed infection empyema, and severe constitutional symptoms were the rule. These persisted until the institution of intercostal drainage.

In one case tuberculous empyema and bronchopleural fistula were present prior to operation, and this case is, therefore, not included in the above tabulation. This was the desperate case of a young girl, and it was thought that adhesions might be holding open the fistula. Severance of the adhesions was tried in the hope that it might permit the fistula to close. The patient was febrile preoperatively and remained so thereafter. She went downhill and died in a few months. It cannot be said that pneumonolysis contributed to the poor result in this case.

The development of tuberculous or mixed infection empyema following thoracoscopy or pneumonolysis is a serious complication indeed. The subsequent fates of the 16 patients so affected will be summarized briefly to illustrate this point. Four of the patients with tuberculous empyema and 6 of the patients with mixed infection empyema died immediately or later. An additional patient died after five years, and this late death may be connected with the empyema experienced at the time of operation.

*Case 16:* A white man of 22 had artificial pneumothorax for a large left upper lobe cavity. He developed a small amount of serous negative effusion prior to pneumonolysis. Pneumonolysis was done on December 13, 1937. It was "partial" and had to be stopped due to bleeding from the operative site. Subsequently he developed a serosanguineous effusion which was negative on smear and culture for tubercle bacilli. The effusion resorbed practically completely and the patient was deemed to be ready for a second stage operation. Before this could be carried out he developed a sudden increase in effusion with a temperature of 102°F, on January 11, 1938. The next day aspiration showed the fluid to be clear, but to contain tubercle bacilli on smear. The fluid reaccumulated after aspiration, although the patient's temperature quickly returned to normal and obliterative pleuritis set in. The pulmonary cavity, however, which had been open until the onset of

the second effusion closed shortly thereafter and remained closed. The fluid became cloudy but never thick. The last aspiration was done in January, 1939. This specimen still showed tubercle bacilli on smear. The patient was discharged on March 27, 1939 as arrested. X-ray film at the time of discharge showed a thin veiling over the upper and outer half of the left lung field, such as is commonly seen with residual effusion, thickened pleura or both. He remained well and worked eight hours daily until June, 1941. At that time he developed a recurrence of empyema with a bronchopleural fistula. His tuberculosis spread extensively throughout both lungs and he died on October 1, 1942 with far advanced bilateral tuberculosis, tuberculous empyema and bronchopleural fistula.

Of the 7 patients who developed tuberculous empyema, 2 died shortly following this complication, one within two months and one within one and one-half years. Both had extensive bilateral tuberculosis, but the development of tuberculous empyema undoubtedly made their prognosis entirely hopeless and hastened their death. Three patients eventually improved sufficiently so that thoracoplasty could be done, but in all 3 thoracoplasty had to be done over a residual empyema and an only partly reexpanded lung. All 3 did poorly. One case is still in the hospital. He had a two-stage thoracoplasty and one revision. He developed tuberculous cutaneous sinuses following the last operation. His case is also complicated by tuberculous bronchitis. At present, his condition is poor. He has been observed over a five-year period following the original pneumonolysis. One patient developed a bronchopleural fistula shortly before his second-stage thoracoplasty was done, and he died four days postoperatively of aspiration of the contents of his empyema cavity into both lungs. One patient had numerous operations, but he retained a residual empyema cavity which had to be aspirated even after extensive thoracoplastic operations. He died of amyloidosis. The sixth patient's history (case 16) has been given above, another unfavorable result. Only one out of the 7 patients could be salvaged. His lung reexpanded following aspiration and irrigation treatment and he was reported well and working after four years. This last patient is one of the 2 in whom thick pus was never observed, and this may have contributed to the eventual good result.

The patients in whom mixed infection empyema developed did equally poorly. Five out of these 8 patients were dead within six months. All had immediate thoracotomies, and one patient reached the thoracoplasty stage, but died after the first stage of general debility. The sixth patient died three years postoperatively. She retained a draining thoracotomy wound through these years and died of uncontrolled empyema and progression of her disease in both lungs. In the seventh patient thoracoplasty could be performed following thoracotomy. Although his sputum is alternately positive and negative, and although he developed amyloidosis, his present condition, three years following pneumonolysis, is fair.

The eighth case is of interest because of his unusual course, and the end result, to date, appears good.

*Case 196:* A 34 year old white man had pneumothorax induced for a moderately ad-

vanced tuberculosis of the right upper lobe. Complete pneumonolysis was performed on August 8, 1941. His temperature rose to 101°F. postoperatively and he developed fluid. This was slightly bloody and negative for tubercle bacilli on smear and culture. His temperature remained elevated for one week and then returned to normal. Nine days later, on August 25, 1941, he developed a chill and his temperature rose to 102°F. Fluid was noted to have increased, and aspiration on August 26, 1941, showed a gram-positive coccus on smear which did not grow out on culture. Tubercle bacilli were absent. His general condition remained good, though febrile, and conservative treatment with various antiseptic irrigating solutions was instituted. The gram-positive coccus was seen occasionally, and culture, on some occasions, showed *Staphylococcus aureus*. On September 23, 1941, cocci were isolated for the last time, and the temperature became normal. On October 24, 1941, tubercle bacilli were first isolated on culture. From then on the fluid continued to contain tubercle bacilli, eventually even on smear. He developed obliterative pleuritis, but pneumothorax refills were continued until April, 1942. On the basis of manometric readings, a small pleuropulmonary fistula was then demonstrated, and air refills were discontinued. The space soon filled with reexpanding lung and a small amount of fluid which was tapped diagnostically from time to time. It remained clear, though positive. He was discharged as arrested in December, 1942, and, although he is reported to be well and working four years after pneumonolysis, it is not known whether he still has residual fluid or whether it has been aspirated recently.

The patient who developed a pure staphylococcus empyema following pneumonolysis did well. His lung reexpanded fully following thoracotomy drainage, and his condition became arrested on further sanatorium care. He remained well and worked four and one-half years later.

#### OTHER COMPLICATIONS

*Subcutaneous emphysema:* This was seen frequently in a mild degree, occasionally in a moderate degree. Mediastinal emphysema was never observed. The pneumothorax was never lost, and no special treatment was ever required or given.

*Radial nerve paralysis:* One patient developed paralysis of the radial nerve. This was due to the peculiarity of position in which the arm was secured during operation. He received physiotherapy and the condition cleared up completely after three weeks.

*Obliterative pleuritis:* The development of positive pressure pneumothorax and obliterative pleuritis was not infrequently seen, and it occasionally shortened the period of pneumothorax treatment. Some of these patients were given oleothorax for maintenance of the space. However, the patients who did not receive this treatment and in whom the lung was permitted to reexpand, when it showed a tendency to do so, did fully as well. It is also surprising how many of the "obliterating pneumothoraces" can be maintained indefinitely with small refills and relatively high pressures. Many a patient was discharged with the notation "obliterating pneumothorax," and follow-up showed that he was still receiving pneumothorax three and four years later.

## FINAL RESULTS

## 13: Deaths directly attributable to operation

	DEATH WITHIN SIX MONTHS	LATER DEATH	PER CENT
Group 1—88 pneumothoraces.....	2	1	3.6
Group 2—102 pneumothoraces.....	2	4	6.1
Group 3—24 pneumothoraces.....	—	—	—
Group 4—101 pneumothoraces.....	—	1	1.0
Total (on basis of 401 operations).....	4	6	2.5
Deaths calculated on basis of 302 patients.....			3.3
Deaths calculated on basis of 315 pneumo- thoraces.....			3.2

All these deaths were attributable directly or indirectly to empyema, and all but one death occurred in groups 1 and 2. The death in group 4 is one of the cases in which it cannot be decided whether they should be included in the group of postoperative empyema.

*Case 20:* A 26 year old white man had artificial pneumothorax induced on June 19, 1937, for far advanced tuberculosis of the right upper lobe. First-stage pneumonolysis was done on July 2, 1937, and some adhesions were cut. He was admitted to Montefiore Hospital on September 9, 1937, with an ineffective partial pneumothorax and positive sputum. He had a small amount of fluid, but was afebrile. Fluid was not aspirated, and on January 17, 1938, thoracoscopy was done. The lung was found broadly adherent and nothing was cut. The temperature became elevated to 101°F. on the third postoperative day. It became normal on the fifth day and remained so thereafter. It was decided to reexpand the lung and prepare the patient for thoracoplasty because pneumothorax was ineffective. Refills were immediately discontinued. A small amount of fluid was observed, but it was believed to be *ex racuo*, and no aspiration was done until March 9, 1938. The fluid was clear, amber and positive for tubercle bacilli on smear. It slowly became thick and the patient was treated with intrapleural aspirations and irrigations. This patient eventually died, following the development of amyloidosis and numerous operations for eradication of the empyema cavity. One may speculate whether this patient would not have developed empyema even if thoracoscopy had not been done.

## 14: Total deaths (502 patients)

Due to operative procedure.....	10 (11 ?—see case 16)
Progression of disease.....	22
Extrapulmonary tuberculosis.....	1
Cardiac.....	1
Accidental drowning.....	1
Carcinoma of stomach.....	1
Postoperative lobectomy.....	2 (1 at Montefiore, 1 outside)
Total deaths.....	38, or 12.6 per cent

## 15: Unfavorable results (502 patients)

No change.....	10
Progression.....	20
Total.....	30, or 9.9 per cent

Follow-up shows that 4 of the cases listed as "no change" and one out of the 20 listed under "progression" subsequently did well. These patients left the institution against advice and sought treatment elsewhere. All had additional treatment, and their condition became arrested.

*Favorable results:* The remainder of the patients were listed as improved during the period of hospitalization. The total figure of 234 is not identical with the figure of 251 in tabulation 3 under "good results," because tabulation 3 refers to pneumothoraces rather than patients, and because it also includes good results on the operated side, regardless of the condition of the contralateral lung. In a few cases it was the uncontrolled disease of the contralateral lung which determined the eventual outcome.

16: *Favorable results (502 patients)*

	NUMBER	PER CENT
Arrested, well, working or able to work.....	201	66.5
Improved, able to work.....	13	4.3
Improved, unable to work.....	5	1.7
Improved, still hospitalized.....	15	5.0
Total favorable results.....	234	77.5

It is known however that, out of 219 patients discharged as arrested or improved, 18 have been readmitted to date, or have been reported to have broken down. Five out of these 18 have died at this writing. One of these cases, no. 16, was reported above.

17: *Length of observation following operation*

Less than 6 months.....	11
6 months to 1 year.....	11
1 to 2 years.....	20
2 to 3 years.....	72
3 to 4 years.....	80
4 to 5 years.....	60
5 to 6 years.....	33
6 years plus.....	15
Total.....	302

All but 42 patients, or 13.9 per cent, have been observed for from two to more than six years. While this observation period is not long enough to study the course of pulmonary tuberculosis, it appears quite sufficient to study the results of pneumonolysis which is, after all, only one phase in the treatment of an extremely chronic disease.

# DISCUSSION

If an attempt is made to compare this series with some of the more recent ones in this field, one is struck by the fact that more patients had simple thorascopies done in our institution than in other hospitals. In our series, 101 out of 315 cases,

or 32 per cent, had their pleural cavity inspected and nothing was cut in them. In a recent series by Jones, 49 out of 450 patients, or 10 per cent, had simple thorascopies. In Newton's series, the corresponding figures are 20 patients out of 166, or 12 per cent. In a study by Stemmerman and Tchertkoff, the figures are 23 out of 151, or 15.2 per cent. This difference in policy may be more apparent than real. In order to draw the correct conclusions from the above figures one would have to know what proportion of all patients in whom pneumothorax was induced over a given period of time was subjected to thorascopy. In Jones' series it is stated that 42 per cent of all patients in whom pneumothorax was induced were thorascoped. While this figure is not available for the present series, it has been compiled for the years 1943 and 1944 for the Montefiore Country Sanatorium. This study shows that 78 pneumothoraces were successfully induced, and that 49, or 63 per cent, had a thorascopy. We have pursued the policy of subjecting to thorascopy patients in whom the preoperative outlook for lysis was not favorable, because we felt that complications from simple thorascopy were nil. On the other hand, these patients stood a chance to gain from the operation. Inclusion of such patients in our series tends to give the impression that the percentage of simple inspections is very large, whereas actually this is not the case.

Results of pneumonolysis are expressed in different terms by each author and comparisons are possible only after our figures have been translated to a comparable ground. Jones reports "total good results" in 75 per cent. In this he includes "technically and clinically successful," and "technically unsuccessful and clinically successful." The corresponding figure in our series is 163 out of 214 pneumothoraces, or 76 per cent, since it is evident that simple thorascopies must be omitted and only actual pneumonolyses counted, as Jones has done. Stemmerman and Tchertkoff report their cases differently. They find that their conversions are 68 out of 124, or 54 per cent. The corresponding figure in this series is 49 per cent. Newton reports his cases as "clinically successful" in 87.6 per cent. The corresponding figure in this series is 76 per cent. It is evident, then, that our figures fall into the general range of averages, although Newton's series shows good results which have not been duplicated elsewhere.

The incidence of postoperative hemorrhage seems to be subject to wide variation. Newton reports no cases of mild or severe bleeding, and the incidence in Stemmerman and Tchertkoff's series is also zero. Jones reports an incidence of 4.9 per cent, and Goorwitch reports 9 per cent. The incidence in this series is 1.7 per cent.

Our incidence of postoperative empyema also falls within the general range. This series has 16 out of 401 operations, an incidence of 4 per cent. Jones' series shows 2.6 per cent, and Stemmerman and Tchertkoff's series 4 per cent. The latter authors have, as we do, one case which occurred in a patient in whom a simple thorascopy was done. Goorwitch's series shows an incidence of 6.3 per cent, but this figure is high because it is not strictly comparable. Only actual pneumonolyses and no simple thorascopies are included in his group, and this necessarily would raise his percentage. Newton's results in this respect are again without duplicate inasmuch as he has no postoperative empyema. His

careful selection of cases according to strict indications accounts for his good results.

It is significant that, in the years 1937 to 1939, 128 operations were performed with an incidence of postoperative empyema of 8.6 per cent, and that, in the years 1940 to June, 1943, 273 operations were done, and the incidence of postoperative empyema was only 1.8 per cent. The difference is due to at least two palpable factors. From the physician's point of view, the indications were restricted for the induction of pneumothorax. Certain far advanced, obviously hopeless cases were no longer approved for pneumothorax therapy and consequently did not come to thoracoscopy. This automatically excludes a group in which complications are necessarily high. The surgeons, on the other hand, have gained experience and perfected their technique so that they now know exactly how much pneumonolysis can be combined with a high degree of safety.

The fatal outcome of tuberculous and mixed infection empyema in our series is so high that one is forced to conclude that tuberculous empyema following pneumonolysis is more serious than empyema complicating pneumothorax therapy without operative intervention. It seems that one is more successful in dealing with ordinary empyema, and that lungs can more readily be re-expanded and thoracoplasty done. The reason may be that when empyema follows pneumonolysis it is probably due to injury of a pulmonary tuberculous focus by the electrode, or to an extension of the slough into a tuberculous cavity.

Although the incidence of tuberculous empyema in all our pneumothorax patients has not been compiled, this figure is again available for the small series of 78 patients treated with pneumothorax in the Country Sanatorium during 1943 and 1944. Out of 78 cases in whom pneumothorax could be induced, 4 developed tuberculous empyema, and one staphylococcus empyema, and in only one tuberculous empyema case had pneumonolysis been done in the proper time relationship so as to be regarded as a complication. The other 3 cases developed empyema from six months to one and one-half years after pneumothorax induction. Although these figures are rather small to permit calculation of percentage incidence, it is seen that the incidence of empyema was three times as high in the group without pneumonolysis than in that following pneumonolysis, a percentage of 3.8 and 1.3, respectively. The administration of pneumothorax itself, then, is beset with serious complications, and this fact ought to be considered before judgment is passed on the high incidence of empyema following lysis.

It does not appear necessary or desirable to aspirate all postoperative effusions in a routine fashion. Only a small proportion of our patients were aspirated, and less than 50 per cent of these showed positive bacteriological findings. It is likely that all these effusions are tuberculous and the demonstration of tubercle bacilli is determined by the limitation of our bacteriological methods. A transitory effusion, or one that shows a tendency to decrease, need never cause concern, even if accompanied by temperature elevation. If the effusion persists, a certain percentage may be expected to develop empyema later on. This percentage does not appear to be higher than can be expected during the course of pneumothorax therapy in general.

We have been particularly interested in including those patients in the tabula-



tion on whom thoracoscopy only was done. The question arises how justified the physician is in recommending that adhesions be cut. The surgeon has to ask himself what chances he may take when he inspects the adhesions on the operating table. If one follows group 4 through all tabulations, it is at once evident that, as a whole, this group did not fare much worse than the others. Although favorable results attributable to the operation were obtained only in 20.8 per cent of group 4, even this figure is significant. It is surprising that a considerable number of cases seem to have sputum conversion postoperatively although nothing was cut. Conservatism in operating is even more advisable if this group is followed during the rest of their hospitalization. More than half of the entire group, 54.5 per cent, is found in tabulation 2 "favorable results not directly attributable to operation." Fully 12 per cent did well, although no treatment other than discontinuation of pneumothorax and sanatorium treatment was given. This result was, of course, not anticipated and reexpansion was undertaken with later thoracoplasty in view. In the final outcome little difference is discernible in the four groups:

*Eventual good result (315 pneumothoraces)*

Group 1.....	87.5 per cent
Group 2.....	79.4 per cent
Group 3.....	70.9 per cent
Group 4.....	75.2 per cent

The importance of urging caution in pneumonolysis is further emphasized by a glance at the incidence of postoperative empyema, and deaths attributable to operation. All but one empyema, and all but one death, occurred following complete or partial pneumonolysis.

These considerations cannot be carried to the point where one might ask: Why do pneumonolyses at all? The incidence of progressive tuberculosis in group 1 is only 5.7 per cent as compared to 20.8 per cent in group 4. Also, patients in whom successful pneumonolysis is done have a better chance to escape thoracoplasty and their hospital stay is thereby shortened, not to mention the fact that thoracoplasty is distasteful to most patients who might get away with pneumothorax. Another point is that the number of patients who were negative preoperatively is somewhat higher in group 4, as one is disinclined to recommend hazardous operations in the negative patient. However, the good result and the lesser risk of thoracoplasty as compared to pneumothorax have been pointed out by those who advocate primary thoracoplasty for many patients in whom pneumothorax is usually performed. Finally, one gains the distinct impression that a complete pneumothorax can be carried along easier after the patient's discharge from the institution, and these patients are less subject to effusions, empyemata and recurrence of active disease.

The question if and when pneumonolysis should be done is, then, a very delicate problem which can only be decided from case to case by close coöperation between physician and surgeon. It is now our practice to subject all pneumothoraces to thoracoscopy unless they show an obviously inoperable condition

with complete surface adhesions over the involved area, or unless there are very definite indications why pneumothorax should be abandoned immediately, such as ballooning of a cavity. The figures for 1943 and 1944 are again available and instructive. Only 11 out of 78 pneumothoraces, or 15 per cent, were given up without the benefit of thoracoscopy for one or the other of the above named reasons. Another 15 per cent were given up for other reasons, such as empyema, contralateral progression and excessive dyspnea. Seven per cent did not require pneumonolysis because they had no adhesions, and 63 per cent were thoracoscoped. It is our practice to do a thoracoscopy on all cases showing adhesions, whether the sputum is negative or positive. Although, in the earlier years, many months, at times, elapsed before the patient came to operation following pneumothorax induction, it is now our aim to operate as soon as the space is sufficiently large, if possible, within three or four weeks of induction. If an effusion is present preoperatively, it must be stationary or decreasing, and the patient must be afebrile before the case is operated on. In rare cases febrile patients are operated on, but these patients are special problems.

One gains the impression from a review of the literature that the most dangerous type of operation is the one in which adhesions are partially cut. These operations are included in our partial pneumonolysis group, although this group also contains cases in which some key adhesions were completely cut while others were left. Certainly the incidence of persistent effusions and tuberculous empyemata is highest in the partial operations. Mixed infection empyema is more common in the complete type of operation, but the figures are so small that even one case makes the difference between the highest incidence and the second highest, and certainly no definite conclusions should be drawn from them.

#### SUMMARY

The records of 302 consecutive patients who were subjected to thoracoscopy during the course of treatment for pulmonary tuberculosis were analyzed. It was found that 40 per cent of the pneumothoraces were benefited by the operative procedure directly, while another 39.7 per cent did well during the later course of observation, some by the institution of other treatment. Serious complications were generally due to the development of postoperative empyema, the incidence of which was 4 per cent in 401 operations. Ten out of 16 patients who developed empyema died, an incidence of 3.2 per cent for the total number of patients. This emphasizes the seriousness of an operation generally regarded as minor. We feel that a conservative attitude in approaching adhesions is justified. The other complications of the operation are discussed and the present plan of integrating pneumonolysis in the collapse therapy program in this institution is outlined.

#### SUMARIO

Analizanse los protocolos de 302 enfermos consecutivos en los que se realizó la torascocopia durante el tratamiento por tuberculosis pulmonar. Un 40% fueron beneficiados inmediatamente por el procedimiento operatorio, en tanto

que en 39.7% la mejoría tardó algún tiempo en presentarse y en algunos hasta aplicárseles otro tratamiento. Las complicaciones graves debieronse principalmente a la formación de empiema postoperatorio, cuya incidencia resultó de 4% en 401 operaciones. Murieron 10 de los 16 enfermos que manifestaron empiema, o sea una incidencia de 3.2% para el total de enfermos, lo cual recalca la gravedad de una operación considerada generalmente como de menor importancia. En el tratamiento de las adherencias está, pues, justificada una actitud conservadora. Discútnense las otras complicaciones de la operación y el plan actual de incorporar la neumonolisis en el plan de colapsoterapia en la institución de los AA.

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# VACCINATION WITH THE VOLE BACILLUS (WELLS)<sup>1</sup>

## Protective Value of Percutaneous and Intracutaneous Vaccination (Observations on Multiple Puncture Vaccination on Man)

KONRAD BIRKHAUG

Following our first experimental series on the protective value of the vole bacillus (Wells) as compared with the BCG vaccine against tuberculous infection in the guinea pig (1), in which we demonstrated that the vole bacillus gave a high degree of protection which was equal to, but not greater than that produced by vaccination with the BCG vaccine, we set out to compare the protective value of the multiple puncture (Rosenthal's method (2)) and intracutaneous vaccination of guinea pigs with the vole bacillus. This was followed by a small series of multiple puncture vaccinations on man with the vole bacillus.

*Animals:* Thirty-six normal albino guinea pigs, which did not react to 10 mg. tuberculin intracutaneously, and weighed approximately 470 g.  $\sigma = 36.15$  g., were divided in three equal groups, each containing 6 male and 6 female animals. Our animals were carefully selected from a strain which had proved unusually resistant to intercurrent infection. The housing and feeding conditions were identical for all the animal groups.

*Immunization:* The *multiple puncture group* of animals were vaccinated as follows: the animal was held tightly and the depilated skin on the right side of the body was washed with 70 per cent ethyl hydrate and then with ether. A few drops of a freshly prepared saline suspension of a four weeks old Dorset culture of the vole bacillus, containing 5 mg./ml. bacilli by exact weight, were spread evenly over the defatted skin area with a long needle. Our 40-needled automatic snapper vaccination apparatus (3) was pressed tightly against the stretched skin and the needle-plate was released by pressure on a button. The needles pierced the skin to a depth of about 2 mm. Small petechial hemorrhages appeared in the punctures when the skin was stretched. A few more drops of the bacillary suspension were spread over the punctured area and the vaccine was allowed to dry in the course of a few minutes. No bandage was applied to the vaccinated area.

The *intracutaneous group* of animals was injected quite superficially with 0.1 ml. of a suspension containing 0.5 mg./ml. vole bacilli. The injection was made on the right side of the depilated and washed body.

The *control group* was left intact.

*Vaccination reactions:* The multiple puncture group showed a doubtful reaction one week later, while the intracutaneous group presented a red papule measuring on the average 6 mm. in diameter and was elevated several millimeters. Two weeks after vaccination the multiple puncture group presented uniformly a circular pattern of 40 red papules measuring approximately 2 to 3

<sup>1</sup> From the Department of Medical Research, Chr. Michelsen Institute, Bergen, Norway.

mm. in diameter and raised a few millimeters. No desquamation, pus formation nor degeneration was visible. The intracutaneous group presented 1 cm. wide greatly inflamed papules, darkly brown in color and necrotic in the centre. The adjoining axillary and inguinal lymph nodes were palpable in both groups. One month after vaccination the multiple puncture papules were still larger and more elevated, without any marked pus formation in the punctures. The underlying tissue was now considerably thickened and the adjoining axillary and inguinal nodes had become pea-sized. The intracutaneous group had mostly formed suppurating abscesses with markedly thickened edges and infiltrated underlying tissue. The adjoining axillary and inguinal nodes were of similar size as in the multiple puncture group. Two months after vaccination the multiple punctures were still visible and palpably infiltrated. Desquamation was in progress and the inflammatory reaction was rapidly receding. The intracutaneous group presented healed vaccination lesions with nearly normal suppleness of the skin. The adjoining axillary and inguinal nodes were markedly enlarged and firm to touch in all the vaccinated animals. They persisted longer in the multiple puncture group than in the intracutaneous group and were palpable in the former as long as nine months after vaccination.

*Postvaccination tuberculin reactions:* The tuberculin tests were made with 10 mg. tuberculin intracutaneously. The reading was made forty-eight hours later and our minimum requirement for a positive reaction was an induration measuring crosswise 10 mm. and when the skin was folded upon itself 4 mm. Half of this thickness multiplied by the two diagonal diameters of the indurated area should give us the approximate volume of the indurated area, as for example:  $2 \times 10 \times 10 = 200 \text{ mm}^3$ .

One month after vaccination each animal in both groups reacted to tuberculin. The average reaction was 1,009 mm.<sup>3</sup> induration and 33 mm.<sup>2</sup> central necrosis in the multiple puncture group and 646 mm.<sup>3</sup> and 15 mm.<sup>2</sup>, respectively, in the intracutaneous group. Three months later the multiple puncture group gave 2,043 mm.<sup>3</sup> induration and 78 mm.<sup>2</sup> central necrosis and the intracutaneous group 1,592 mm.<sup>3</sup> and 56 mm.<sup>2</sup>, respectively. It is quite apparent that the strongest allergy was produced by the multiple puncture method. The difference between the two groups was statistically significant at both times.

*Virulent test inoculation:* Ninety days after the vaccination with the vole bacilli, all animals in the multiple puncture, intracutaneous and control groups were inoculated subcutaneously in the left leg with 0.000,01 mg. (by culture 146 viable) human virulent tubercle bacilli ("Tuxen"). This dose killed the average guinea pig in approximately 200 days.

*Postinfection tuberculin reactions:* Two months after the virulent inoculation, intracutaneous tuberculin tests were done with 10 mg. tuberculin on all the animals. Two days later we found that all the controls had become strongly positive and the immunized animals reacted uniformly positive. The control group showed an average induration of 2,316 mm.<sup>3</sup> and central necrosis 289 mm.<sup>2</sup>, the multiple puncture group 1,945 mm.<sup>3</sup> and 94 mm.<sup>2</sup> and the intracutaneous

group 2,106 mm.<sup>3</sup> and 124 mm.<sup>2</sup>, respectively. It is perhaps presumptuous to read into the differences in reactivity towards tuberculin that the virulent tuberculinization progresses slowest in the multiple puncture group. This supposition must await later verification.

*Postinfection weight curves:* Chart 1 depicts the average weight curves for the three groups of animals for the duration of the experiment. It becomes quite apparent that the multiple puncture group fares best and its weight curve follows the normal growth increments for guinea pigs, with notable exceptions for 4 animals which lost weight towards the end of the experiment. But the intra-

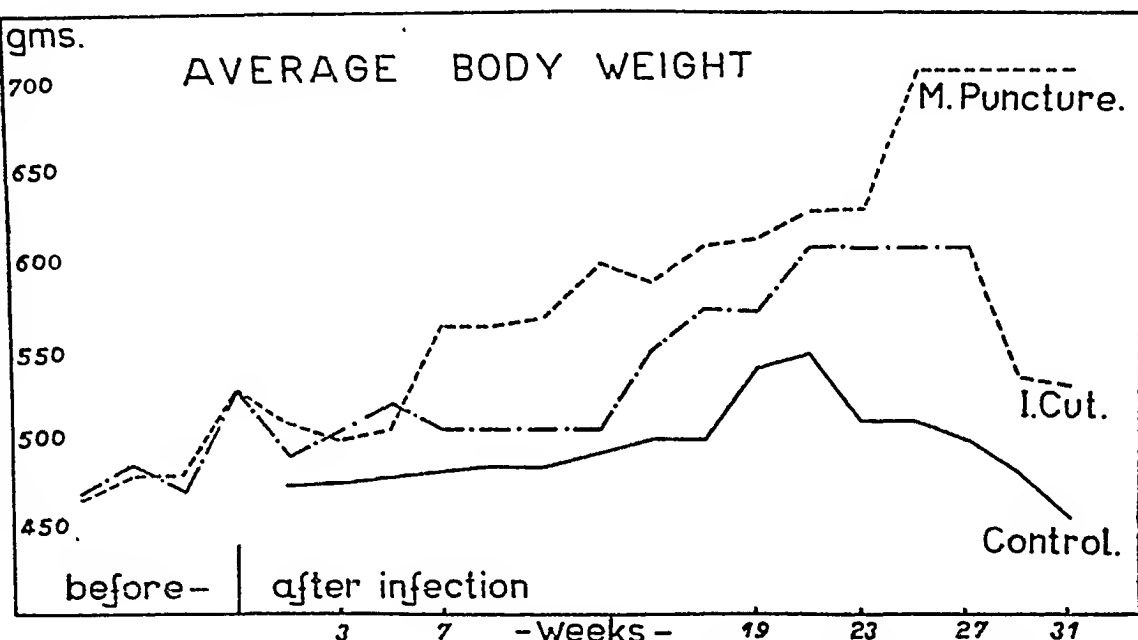


CHART 1. Average weight curves of 12 animals in each of the vole bacillus vaccinated and the control groups.

cutaneous group began to lag behind the multiple puncture group from the seventh postinfection week.

*Mortality:* The first control animal died of generalized tuberculosis 109 days after the virulent inoculation and the last animal 257 days after inoculation, with an average longevity of 187 days for the control group. Only one multiple puncture group animal died spontaneously of generalized tuberculosis 247 days after the virulent inoculation. Four animals in the intracutaneous group died spontaneously of generalized tuberculosis 242, 257, 264 and 265 days, respectively, after the virulent inoculation. The remaining surviving animals were killed between 265 and 270 days after the virulent inoculation in order to compare the degree of tuberculosis with those of the spontaneously dead animals.

*Macroscopic tuberculous involvement:* By making use of the macroscopic scoring

TABLE 1

*Comparative statistical analysis of significant deviations in vaccinated groups placed against the control group*

ORGANS	MULTIPLE PUNCTURE GROUP			INTRACUTANEOUS GROUP			CONTROL GROUP
	Average	t	P	Average	t	P	Average
Lymph nodes							
Knee left ml.....	0.10	1.536	0.15	0.12	1.392	0.20	0.37
Knee right ml.....	0.01	3.628	<0.01	0.10	0.612	0.55	0.05
Sup. inguinal left ml.....	0.48	3.993	<0.01	0.61	2.819	0.01	1.36
Sup. inguinal right ml.....	0.15	3.520	<0.01	0.31	0.779	0.45	0.38
Deep inguinal left ml.....	0.09	2.041	0.06	0.12	1.727	0.10	0.24
Deep inguinal right ml.....	0.01	3.675	<0.01	0.06	1.306	0.25	0.10
Femoral left ml.....	0.22	3.239	<0.01	0.42	1.352	0.25	0.63
Femoral right ml.....	0.18	2.812	0.01	0.37	0.794	0.45	0.49
Cervical left ml.....	0.20	2.844	<0.01	0.18	2.825	<0.01	0.48
Cervical right ml.....	0.17	2.572	0.02	0.17	2.572	0.02	0.38
Trach. bronch. left ml.....	0.40	4.126	<0.01	0.64	2.827	<0.01	1.04
Trach. bronch. right ml.....	0.35	4.150	<0.01	0.55	2.811	0.01	0.96
Axilla left ml.....	0.19	2.246	0.05	0.26	1.311	0.20	0.38
Axilla right ml.....	0.17	3.724	<0.01	0.19	4.123	<0.01	0.36
Spleen g.....	2.0	3.185	<0.01	2.9	0.745	0.45	3.6
per cent.....	0.3	4.900	<0.01	0.5	2.929	<0.01	0.9
Liver g.....	43.9	2.450	0.04	28.8	0.816	0.40	35.5
ml.....	44.4	2.597	0.03	38.2	0.581	0.60	35.8
per cent.....	5.8	4.973	<0.01	6.9	2.400	0.03	8.5
Lungs g.....	9.6	2.835	<0.01	10.9	1.808	0.10	14.0
ml.....	10.2	4.432	<0.01	12.6	2.910	<0.01	17.8
per cent.....	1.4	5.684	<0.01	1.8	4.454	<0.01	3.4
Total lymph nodes g.....	4.1	5.532	<0.01	6.6	3.645	<0.01	13.0
per cent.....	0.6	8.749	<0.01	1.2	5.676	<0.01	3.1
Efficiency per cent.....	75.0			41.7			

*Note:* Significant deviations from the control group are italicized.

of tuberculous involvement in the guinea pig elaborated by Petroff and Steenken (4), we found the following:

Tuberculosis:	++++	+++	++	+	0
Control group:	11	1			
Multiple puncture:	—	4		1	7
Intracutaneous puncture:	5	1	2	1	3

It is quite apparent from the macroscopic examination of the spontaneously dead and killed animals that an absolute immunity against a virulent tuberculous inoculation is not generally produced by vaccination with the vole bacillus,

neither by the multiple puncture nor by the intracutaneous modes of administering the vaccine. But the most effective prolongation of the process of tuberculation was observed in the multiple puncture group, although the intracutaneous group showed a considerable protection.

As on previous occasions we have chosen the quantitative approach for assessing the difference in tuberculous hyperplasia in the variously vaccinated animals, as it must be readily admitted to be more objective than the less exact subjective description of the degree of tuberculous involvement in terms of one or more pluses.

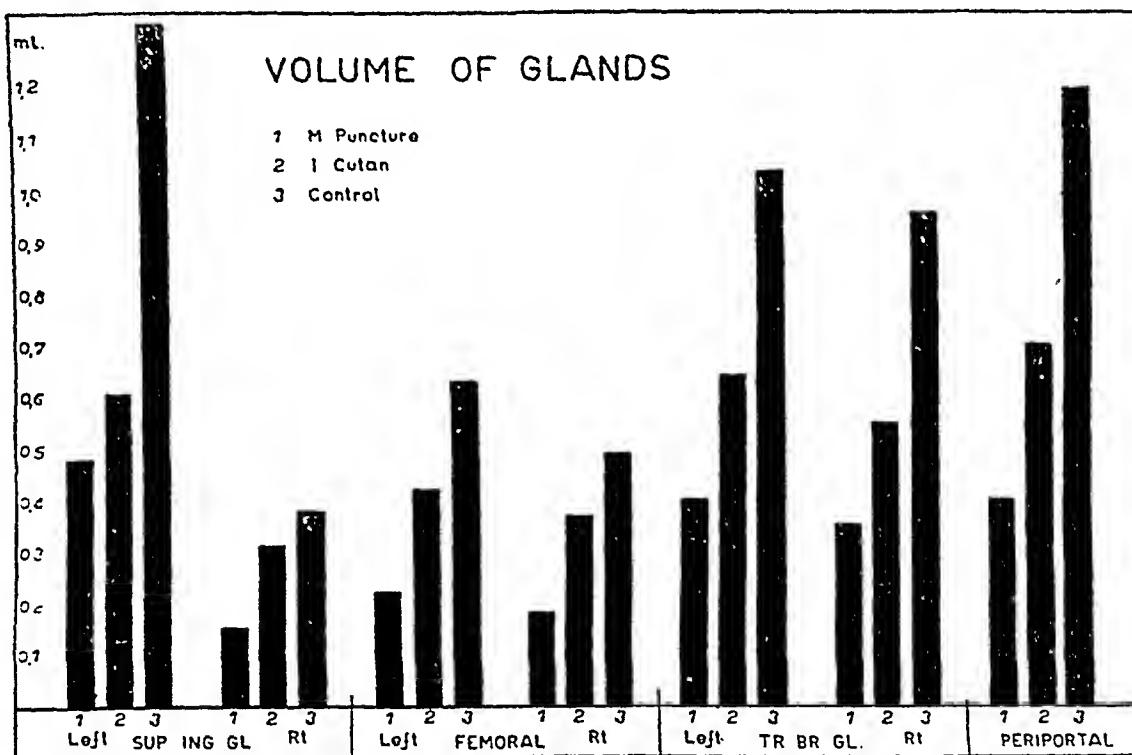


CHART 2. Average volumes (ml.) of various lymph nodes in the vole bacillus vaccinated and control groups of animals.

*Quantitative assessment of tuberculous hyperplasia:* The procedure of determining the exact volume (by water displacement) of the various lymph nodes and viscera, the actual weights of the pooled lymph nodes as well as of the spleen, liver and lungs, and conversion of these weights into percentage of the animal's body weight, has been described in our previous articles (5). The statistical analysis of these complete data was done by the method for comparison of two comparable means ( $\bar{x}$  and  $\bar{y}$ ) by Fisher (6). We have again chosen to reject as insignificant any mean value of  $P$  (probability) which exceeds 0.01. The symbol  $P \leq 0.01$  signifies, therefore, that the observed mean deviations bearing



this or smaller values, must be considered to have *absolute statistical significance* and cannot have occurred by chance alone (7). In Fisher's 1938 tables for distribution of  $t$  (quotient expressing the deviation as a multiple of its probable error), we find that  $P \leq 0.01$  requires that  $t \geq 2.819$  when each group contains 12 animals or samples. Every difference having *absolute significance* is italicized in table 1.

In order to facilitate the understanding of the numerical values of the various differences in size of lymph nodes and weights of these and the spleen, liver and lungs in per cent of the animal's body weights, we have reduced these data to

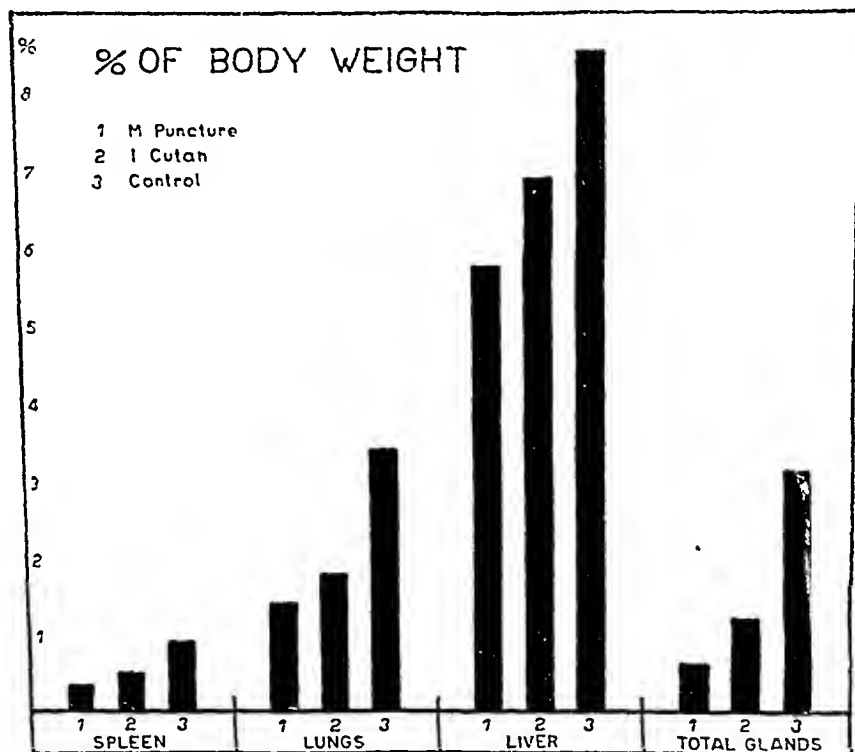


CHART 3. Average weight of spleen, liver, lungs and total lymph nodes (pooled), expressed as per cent of the animal's body weight.

charts 2 and 3. From these we learn that the most effective immunization with the vole bacillus against a virulent tuberculous infection is afforded by the multiple puncture method. The protection offered by the intracutaneous technique is nevertheless considerable. But by and large we learn from the bottom of table 1 that the efficiency per cent is 75.0 for the multiple puncture group and 41.7 for the intracutaneous group when all the assessable factors are taken into account.

From these quantitative data we may conclude that the vaccination with the vole bacillus offers a relatively high protection against a test infection with

virulent human tubercle bacilli and that the multiple puncture method yields results which lie slightly ahead of those observed with the intracutaneous method.

#### MULTIPLE PUNCTURE VOLE BACILLUS VACCINATION IN MAN

Our previous extensive experimentations with the vole bacillus on the usual laboratory animals furnished us with proof of the relative innocuousness of this bacillus. We had likewise obtained significant proofs of the relatively effective immunizing powers of this vole bacillus against a test infection in the laboratory animals with virulent human tubercle bacilli. We were convinced from these experiments, however, that the vole bacillus failed to furnish a greater protection against a virulent tuberculous infection in the laboratory animals than that afforded by the BCG vaccine. In fact we expressed a preference for the BCG vaccine on the ground that its virulence or avirulence offered a slightly greater margin of safety for the laboratory animals than does the vole bacillus when the latter is administered parenterally in greater doses than those recommendable for experimental use. Nevertheless, we felt it urgently necessary to assess the value of the vole bacillus as a vaccine on man inasmuch as we knew that our Swedish colleagues, Wahlgren, Olin and Widström (8) and Arvid Wallgren (9), already had embarked upon such experimentation on humans, on the basis of much less experimental experience with the vole bacillus than we had gained.

With the kind coöperation of the physician-in-chief at the Neevengaarden Insane Asylum at Bergen, Dr. A. Dahlö, we were permitted to vaccinate 18 adult patients who failed to react to 1 mg. tuberculin injected intracutaneously. Twelve were women between 17 and 44 years of age and 6 were men between 17 and 41 years of age. All the patients were in good physical condition and ambulatory (manic-depressive psychoses).

The skin on the lateral aspect of the right arm was cleansed thoroughly with ether. A 4 x 4 cm. sterile cigarette-paper was moistened with a 5 mg. 'ml. vole bacillus suspension in a sterile Petri dish. The paper was placed on the ether-cleansed skin. The cock of our 40-needled automatic vaccination apparatus was drawn up, the end-plate was pressed against the paper while the button was pressed which released the needle-plate. The vaccination was finished and the arm was held tightly in order to stretch the skin and open widely the punctures in the skin. After two minutes' drying of the vaccine, the arm was released and no bandage applied to the vaccinated area.

All the vole bacillus vaccinated patients presented 1 to 2 mm. red papules two weeks afterwards. These increased in size and measured 3 to 4 mm. within one month. Five persons presented a few pustuled papules. No itching nor general indisposition was complained of.

One month after vaccination, the Pirquet scratch test was done on all the vaccinated persons. Two days later 3 patients showed more than 5 mm. infiltration, 12 presented 3 to 4 mm. and 3 approximately 2 mm. infiltration, while one patient did not react at all.

Two months after vaccination the Pirquet scratch test was repeated together with the Mantoux intracutaneous test with 1 mg. tuberculin. All the vaccinated

patients reacted with more than 4 mm. infiltration (average  $5.1 \pm 1.3$  mm.) to the Pirquet test. The Mantoux test with 1 mg. tuberculin gave excessively strong reactions varying from  $17 \times 17$  mm. infiltration to  $32 \times 40$  mm. Beside the nearly vesicular infiltration, many of the vaccinated persons presented a lymphangitic-like rubor which extended far beyond the infiltrated area.

The vaccination papules were now markedly elevated, deeply red and each surrounded by a pink halo. The average diameter was 3 to 4 mm. and the height above the skin surface 1 to 2 mm. Desquamation was already in progress and a few patients showed scabs after the pustules had resorbed. We had a definite impression that the papules were much more angry than those observed after BCG vaccination with 5 mg./ml. vaccine (figure 1).

All the 18 patients were reexamined one year after vaccination. Every one presented deeply brownish-red pigmented papules, measuring approximately 1 to 3 mm. in diameter and 1 to 2 mm. in height. The underlying skin was markedly infiltrated. Some of the papules were capped by a brawny-colored crust. The adjoining axillary nodes were not palpably enlarged, or tender to touch.



FIG. 1. Showing multiple puncture pattern eight weeks after vole bacillus 5 mg./ml. vaccination on man.

The patients had not unduly complained about any itching or tenderness in the vaccinated area. But from the appearance of the papules, it was quite apparent that permanent and pock-like marks would result.

The Pirquet tuberculin scratch test was positive in every one of the vole bacillus vaccinated persons and measured in excess of 4 mm. infiltration (average  $4.9 \pm 1.2$  mm.). The Mantoux intracutaneous test with 1 mg. tuberculin gave uniformly strong reactions varying between  $20 \times 20$  mm. and  $35 \times 45$  mm. infiltration. Vesicular infiltration was present in only 3 patients and the erythematous reactions were likewise markedly reduced from those observed two months after vaccination.

No tuberculous disease was demonstrable in any one of the vole bacillus vaccinated patients.

A control series of 12 women and 6 men of approximately the same age as those employed above was simultaneously vaccinated with 5 mg./ml. BCG by the multiple puncture method. Fifteen of these presented red papules in all the 40 punctures two months afterwards. The papules measured approximately 2 to 3 mm. in diameter and 1 to 2 mm. in height. No pustules were observed.

The Pirquet scratch test was completely negative in 7 persons and only slightly positive (average  $3.4 \pm 1.3$  mm. infiltration) in the remaining 11 persons. The Mantoux intracutaneous test with 1 mg. tuberculin was negative in the 3 persons who presented no lesions at the site of vaccination. The test was positive (more than  $10 \times 10$  mm. infiltration) in the 15 persons who showed vaccination papules. The strongest reaction measured  $27 \times 24$  mm. infiltration. When these 15 successfully BCG vaccinated persons were reexamined one year after vaccination, none presented any visible papules at the site of vaccination. We could barely discern pinpoint white marks in some of the completely healed vaccination papules. The adjoining axillary nodes were in no case palpably enlarged. Most of the BCG vaccinated persons reported that the papules disappeared rapidly three to four months after vaccination.

The Pirquet tuberculin scratch test, done one year after the BCG vaccination test of the 15 successfully vaccinated persons, was wholly negative in 9 and only slightly positive in the remaining 6 (average  $3.7 \pm 0.9$  mm. infiltration). The Mantoux test with 1 mg. tuberculin was wholly negative in 7, slightly positive (5 to 8 mm. infiltration) in 3 persons and positive (more than  $10 \times 10$  mm.) in 5 persons. No tuberculous disease was found in any one of these persons. Revaccination was done in the 7 persons who gave a negative Mantoux test. In 5 of these we observed fully developed BCG papules three to five days after revaccination with 50 mg./ml. BCG vaccine, while normally the papules do not appear before two weeks after vaccination. This accelerated allergic response in spontaneously desensitized BCG vaccinated persons was clearly described by Willis (10) in guinea pigs.

It should be mentioned that we usually employ 50 mg./ml. concentration of BCG vaccine for the multiple puncture method in man in order to obtain approximately 95 per cent positive Mantoux tuberculin tests two months after vaccination and by using 1 mg. tuberculin. In the same series of Mantoux reactors we obtain only approximately 45 per cent positive Pirquet tuberculin scratch tests (11), which proves that the Pirquet test is a much less sensitive detector of BCG vaccination allergy than the Mantoux 1 mg. test.

From the human experiments with the vole bacillus vaccine and the BCG vaccine applied with the multiple puncture method, it becomes quite apparent that the vole bacillus vaccine is considerably more virulent and produces a stronger allergy and more lasting vaccination papules than the BCG vaccine. It is possible that a lesser concentration than 5 mg./ml. of vole bacilli might produce a lower degree of allergy and blemishing vaccination marks. But by and large we cannot escape the impression that the vole bacillus is less suitable as a vaccine on man than the BCG vaccine, which already holds a unique place as a relatively safe and effective prophylactic means against tuberculous disease.

#### CONCLUSIONS

Multiple puncture or intracutaneous vaccination of guinea pigs with the vole bacillus (Wells) produces no absolute but a relatively high protection against a test infection with virulent human tubercle bacilli.

The multiple puncture method of vaccination yields protective results which lie slightly above those observed after the intracutaneous vaccination method.

Multiple puncture vaccination of human adults with the vole bacillus (Wells) produces more permanent vaccination marks and stronger tuberculin reactions than a similar vaccination with BCG, indicating a lesser margin of safety for the vole bacillus as a vaccine for use on man.

#### CONCLUSIONES

La vacunación de los cobayos con la técnica de multipunción o intracutánea con el bacilo del microto (Wells) no facilita protección absoluta, pero sí relativamente alta contra una infección de ensayo con bacilos tuberculosos humanos virulentos.

La técnica de la multipunción da resultados protectores ligeramente superiores a los de la vacunación intracutánea.

La vacunación de los adultos humanos con la técnica de la multipunción con el bacilo del microto (Wells) produce cicatrices más permanentes y reacciones más poderosas a la tuberculina que una vacunación semejante con BCG, lo que indica que el bacilo del microto muestra menos margen de seguridad cuando se emplea como vacuna en el hombre.

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# R1 STRAIN OF TUBERCLE BACILLUS<sup>1</sup>

Its Disinfection and Virulence of Variants in Normal and Silicotic Guinea Pigs

W. STERNBERG, JR. and L. C. GARDNER

Since shortly after its isolation in 1891 the R1 strain of *Mycobacterium tuberculosis* has generally manifested a low but surprisingly constant degree of virulence for guinea pigs (1). Injected subcutaneously in moderate doses it produces poorly visible lesions; only in lymph nodes administered by inhalation it provokes the formation of a limited number of tubercles in the subpleural region of the lung and the hilar lymph node. As a rule these lesions heal by resolution and disappear after twelve to eighteen months, but the associated sensitivity to tuberculin usually persists for longer intervals, gradually decreasing in intensity. Experiments involving infection of silicotic guinea pigs with this strain of mycobacterium have demonstrated that in such animals the infection usually continues to progress, and after two or three years produces a generalized, chronic tubercule (2).

Over the course of years there have been occasional, unexplained exceptions to this general behavior of the R1 strain. Now and then in our own laboratories inhalation infection of groups of 50 to 100 normal or silicotic guinea pigs has produced only weak and transitory skin hypersensitivity to Old Tuberculin and tubercle formation has been rare or apparently lacking. When tubercles did develop they were more apt to be found in the lymph nodes than in the lungs and in silicotic hosts such lesions never progressed. On the other hand, very rarely an exceptional member of a large group of non-silicotic guinea pigs infected by inhalation of this bacillus has developed generalized visceral tuberculosis with fatal outcome. Subinoculation into other guinea pigs of the organisms recovered from the exceptional cases of progressive tuberculosis has produced only the usual self-limited, nonprogressive lesions of infection (3). Other experimenters (4) have likewise reported similar experiences.

Thus, this microorganism, under artificial cultivation for a period of fifty-four years, has ordinarily exhibited a remarkably constant degree of virulence for guinea pigs, well below the level of most freshly isolated tubercle bacilli but still capable of producing caseous lesions. During this period three types of variation in its behavior have been observed: (1) the failure of occasional transplants to produce characteristic reaction in any member of a large group of inoculated animals; (2) the rare instance of generalized, progressive tuberculosis in an isolated member of a large group of guinea pigs reacting in typical manner; (3) the uniform tendency of R1 organisms to continued growth and extension in silicotic guinea pigs.

Changes of the first type have been observed from time to time on attempting to infect groups of 100 or more guinea pigs. Had such results been confined to

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infection administered by inhalation they might be attributed to technical failures but, since simple injection experiments likewise "failed," we are inclined to suspect that the organisms themselves were at fault, for by the latter method they must certainly have been implanted in the tissues. Spontaneous dissociation with persistence of only avirulent dissociants now seems the most likely explanation. Perhaps the commonest cause of such spontaneous dissociation is slight variation in the composition of the culture medium. Evaporation of water with concentration of mineral salts has been found to exert a potent influence. To avoid this possibility we now mark the height of the fluid level upon each container on tubing fluid media; if there has been any evaporation before use, sterile, distilled water is added to make up the deficiency. Whenever such temporary loss of virulence has occurred we have been able to retrieve the more virulent parent strain since stock cultures are transplanted every twenty days in both of our laboratories, the one at the Sanatorium and the other in Saranac Lake.

The rare, isolated case of apparent increase in virulence for normal guinea pigs is probably best accounted for on the basis of variation in host resistance. Cummings (3) demonstrated that the bacteria recovered from such progressive lesions exhibit typical R1 colony structure and produce only normal, self-limited, primary tubercles on subinoculation into other guinea pigs. Others (4) have reported similar results.

The progressive tuberculosis regularly produced by the R1 strain in silicotic guinea pigs is merely a manifestation of the general principle first demonstrated by Gye and Kettle (5) that most types of *Mycobacterium tuberculosis* grow with unusual rapidity in freshly formed silicotic lesions, especially those with necrosis. These investigators proved that human type tubercle bacilli would proliferate without restraint in a silica abscess produced by injecting fine quartz beneath the skin of a white mouse but that, in abscesses produced by chemical irritants like croton oil or turpentine, these bacteria multiply no more rapidly than in normal host tissues. They also showed that small doses of human type tubercle bacilli, which produce only transitory lesions in normal rabbits, cause chronic and ultimately fatal tuberculosis in rabbits with associated silicosis. We extended their observations to include the effects of the low virulent R1 strain upon silicotic guinea pigs. We demonstrated that, regardless of the method of injection, whether by inhalation or by subcutaneous injection, the R1 bacilli would generally produce progressive tuberculosis in guinea pigs *inhaling* quartz dust. We also proved that partially healed R1 inhalation tubercles in the lungs could be reactivated and caused to spread by subsequent exposure to quartz dust (6). We confirmed the observation that other types of tubercle bacilli of full virulence for different animal hosts likewise multiplied more promptly and more abundantly in fresh silicotic lesions; however, the ultimate results were not so striking as with R1 organisms because the virulent bacilli produce progressive disease even without the added factor of silicosis.

A striking exception of this generalization was encountered when we attempted to substitute acid-fast organisms, long under artificial cultivation, which pro-

duced nothing but transitory local abscesses on injection in large doses into normal guinea pigs. Inhalation infection in silicotic guinea pigs was unsuccessful with three avirulent strains: "B2," a bovine strain under laboratory cultivation for twenty-one years; "E. L. T.," one of human origin which had likewise lost all capacity to cause anything but local reaction; and a transplant of BCG, which had been carried on potato ox bile for several years and was incapable of producing progressive lesions. In all three cases the amount of tissue reaction was essentially the same in silicotic as in normal guinea pigs. At the time it was merely concluded that none of these strains had retained sufficient virulence to be influenced by the silicotic environment.

These experiments provided added assurance that the R1 strain differed from others maintained on artificial media for prolonged periods and that it actually maintained a limited degree of virulence which was capable of responding promptly to favorable alterations in environment. This work was done in 1930 when we were exploring the possibilities of dissociation within the animal body. The experiments with completely avirulent strains seemed to prove that growth in silicotic soil would not permit redissociation with the development of virulent variants. It was then decided to explore the possibilities of dissociation in the case of the R1 strain, and Dowd (7) worked for several years in the Saranac Laboratory to learn whether there was evidence to support the hypothesis that silicotic tissue might favor dissociation of R1 microorganisms with a resultant preponderance of virulent variants. He succeeded in demonstrating variation in colony structure in cultures recovered from infected silicotic guinea pigs but these variations were not reproducible on subculture nor did the different types of colony exhibit differences in virulence for animals. All of them produced some self-limited tuberculosis. Unfortunately Dowd used gentian violet egg medium which has subsequently proved most unfavorable for such studies. Shortly thereafter Steenken likewise attempted to dissociate the R1 strain with similar results.

Nevertheless, accumulating evidence continued to suggest that spontaneous dissociation occasionally occurred with this organism as it did with other strains grown for a long time on artificial media. Sometimes a transplant of R1 would produce no more disease in either normal or silicotic guinea pigs than any of the completely avirulent strains. Our problem was to demonstrate evidence of dissociation *in vitro* and to prove that avirulent variants could be produced at will. Using new methods that had been developed in the meantime for dissociating the human strain H37 (8, 9), dissociation was finally accomplished and, through the process of aging, a stable variant was finally obtained that had no virulence for normal or silicotic guinea pigs. The more virulent variant is still obtained only from cultures grown under optimum conditions. It should be pointed out that each of these variants can now be produced at will but that both forms do not develop in the same culture tube; entirely different conditions are necessary for the growth of each. The data which follow deal with the methods by which dissociation was accomplished and results of tests of virulence in normal and silicotic guinea pigs.



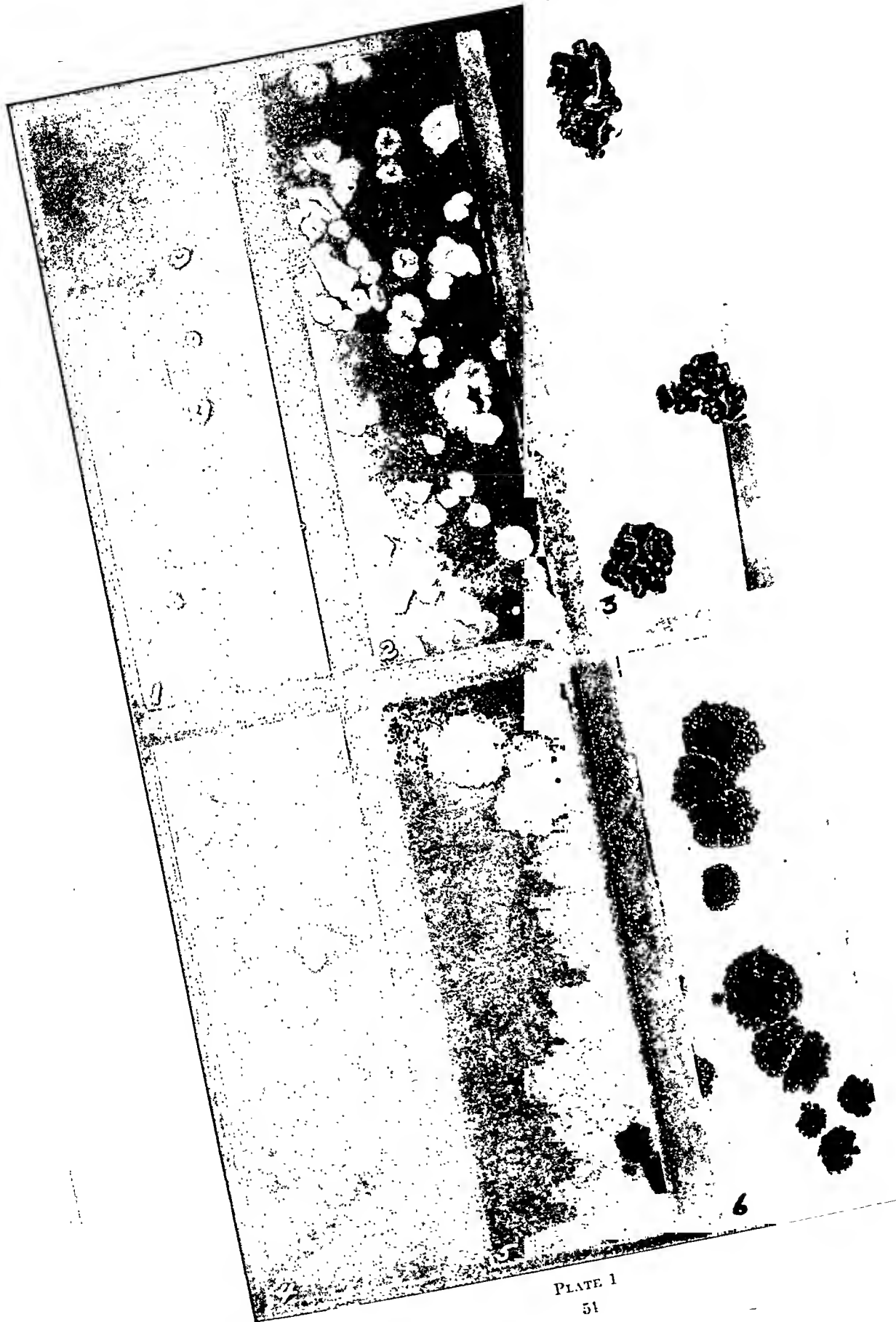


PLATE 1  
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## EXPERIMENTAL DATA

(1) *The virulent variant*: As indicated, this variant normally preponderates in subculture maintained under optimum conditions. These conditions are as follows: The organism is grown on the surface of Proskauer and Beck's fluid synthetic medium of pH 7.0 to 7.2. Best results are obtained if transplants are made every fourteen to twenty days.

Cultures of the organisms should be checked occasionally for colony growth characteristics. This is done by seeding very dilute suspensions of the organisms in physiological saline solution on a solid egg medium. The resulting growths are studied and, if marked changes in colony structure are noted, only those colonies of typical morphology (plate 1, figures 4, 5, 6) are removed and subcultured on Proskauer and Beck's synthetic medium.

As stated before, it is extremely important that the fluid component of the media in the flasks or bottles be maintained at the original level. Any evaporation that has occurred must be made up by the addition of sterile distilled water added under aseptic conditions.

The optimum temperature for good growths is 37.5°C. A proper oxygen and carbon dioxide exchange must be maintained during growth. This can easily be attained by plugging the bottles lightly with absorbent cotton.

(2) *The avirulent or "resistant" variant*: To secure stable colonies of this variant the following procedure has been employed:

Standard cultures of R1 microorganisms were planted on tubes of both Corper's egg-yolk and on Steenken and Smith's medium (10) of pH 6.2. Tubes that exhibited good growth at the end of fifteen days were "aged" by keeping them in the incubator at 37.5°C. for one hundred and fifty days. At the end of this period the parent colonies had lost their original structure and had become transformed into a homogeneous viscid mass. In the midst of this area of lysis, secondary "resistant" organisms had grown to form new colonies. These "resistant" colonies were picked and subcultured on the same kind of media, whereupon they exhibited typical resistant growth characteristics (plate 1, figures 1, 2, 3). The degree of differentiation was more pronounced on Corper's medium than on Steenken and Smith's medium.

In order to be certain that the same phenomenon would occur when growth proceeded from a single cell of the parent R1 culture, a suspension was made

## PLATE 1

FIG. 1. Resistant colony growth Steenken and Smith's medium pH 6.2, thirty-day growth,  $\times 8.5$ .

FIG. 2. Resistant colony growth, Steenken and Smith's medium pH 6.2, forty-five-day growth,  $\times 8.5$ .

FIG. 3. Resistant colony growth, Steenken and Smith's medium pH 6.2, ninety-day growth,  $\times 8.5$ .

FIG. 4. Virulent variant colony growth, Steenken and Smith's medium pH 6.2, forty-day growth,  $\times 8.5$ .

FIG. 5. Virulent variant colony growth, Steenken and Smith's medium pH 6.2, seventy-five-day growth,  $\times 8.5$ .

FIG. 6. Virulent variant spreading colony growth, Steenken and Smith's medium pH 6.2, forty-five-day growth,  $\times 8.5$ .

from a typical R1 colony (plate 1, figures 4, 5) which had been growing on Steenken and Smith's medium for forty days. This suspension was diluted and, using a micromanipulator, a single bacillus was isolated and inoculated upon the same medium. The resultant culture was allowed to age as previously described. Lysis occurred in this single-cell culture as in the parent R1 culture, and, subsequently, it gave rise to the same type of secondary resistant growth.

#### VIRULENCE TESTS IN NORMAL GUINEA PIGS

The *secondary resistant form of colony* from the single-cell strain remained stable for five generations on artificial media. A turbid suspension of such colonies was inoculated into 40 normal guinea pigs—10 subcutaneously, 10 intratesticularly, 10 into the brain and 10 by inhalation. The animals injected subcutaneously developed small caseous tubercles at the site of inoculation, but the area healed in ninety days, leaving no macroscopic evidence of disease. Intratesticular injections likewise produced only local caseous foci which were even smaller than those following subcutaneous injection. Intracerebral injection of 0.5 mg. caused diffuse and focal proliferation of mononuclear and lymphoid cells without caseation. All of these animals remained well and were sacrificed four months after injection. Inhalation infection likewise caused only microscopic foci of proliferation which resolved and disappeared after four months.

The behavior of the resistant variant of R1 was strikingly different from that of the *parent culture* similarly tested in a parallel control series. With the latter, both subcutaneous and intratesticular inoculations produced caseous foci which persisted for a year or longer; and in a few animals disease was found in the liver and spleen. None of the guinea pigs in this series developed progressive disease within a period of eighteen months. Intracerebral inoculation with the parent R1 colonies produced caseous foci in the brain usually followed by death within four months. Inhalation infection produced the usual subpleural tubercles in the lungs, 2 x 2 mm., with caseous centres which persisted up to eight months and then started to retrogress. Aside from extension to the tracheobronchial nodes, there were no extrapulmonary lesions.

#### VIRULENCE TESTS IN SILICOTIC GUINEA PIGS

*Brain.* Ten male albino pigs were given an intracerebral injection of 0.3 cc. of a 1.37 per cent salt solution suspension of 1 to 3 micron quartz particles, a dose equivalent to about 400 mg. of  $\text{SiO}_2$ . At the end of fifty days, 5 of them with a like number of untreated controls were inoculated intracerebrally with 0.5 mg. of the resistant type R1 growth, and the other 5, also with 5 untreated controls, were inoculated with 0.5 mg. of the parent R1 colony. In both silica-tested series the bacilli were administered as near as possible to the area where the quartz had been injected. All animals inoculated with the *resistant type* organisms, both controls and those previously injected with silica, were still living one year later. When killed they showed no macroscopic evidence of disease. The

animals that received the *typical R1* variant plus silica died within two months after inoculation; the nonsilicotic controls injected with the same variant survived for four to five months.

Histologically, the early reaction (thirty-nine to forty-one days) of normal hosts was essentially the same with both variants; it consisted of diffuse and focal infiltrations of mononuclear and lymphoid cells, without evidence of caseation. In animals whose brain had been injected forty-eight days previously with particulate silica, the reaction was much more extensive and there were wide-spread areas of coagulation necrosis.

*Inhalation infection:* In order to confirm these preliminary findings a larger inhalation experiment was performed which involved 103 guinea pigs exposed to crystalline silica in the form of chalcedony (flint). By our customary procedure (11), 75 guinea pigs had been exposed for eight hours a day, six days a week for a period of six months to a dust concentration averaging 100 million particles per cubic foot of air. At the end of this period, 5 were sacrificed to establish the amount of dust reaction, 14 were reserved as further dust controls and 56 were given inhalation infections, half of them with the parent R1 strain and the other half with the resistant dissociant. At the same time, 14 nondusted controls were similarly infected with parent strain R1 bacilli and a like number with resistant dissociants. Twenty-eight of each dusted infected group were returned to the dust room to remain for the balance of their lives while the other half of the two dusted groups were kept with the infection controls in a normal atmosphere. Members of each group were sacrificed at intervals of one and one-half, two, two and one-half, four and six months after infection.

The concentration of dust in this experiment was purposely reduced to about one-tenth of that usually employed in order not to obscure the picture of overwhelming silicotic changes. We probably reduced it too much to produce maximal effects but nevertheless the influence of the silicosis upon the two types of infecting organisms was obvious. At the end of the six months' dust exposure, gross inspection of the microscopic sections revealed no silicotic lesions. This result was anticipated for exposure to ten times the concentration of pure quartz or flint likewise regularly produces no reaction visible on gross inspection. However, with higher atmospheric concentrations enough dust accumulates in the lungs within six months to cause silicotic nodules to develop during the following six months even if the animals are removed to a normal atmosphere. With the comparatively low concentration of 100 million particles per cubic foot of air this did not happen nor did a further exposure of another six months produce *mature* silicosis in the lungs. Nevertheless, the tracheobronchial lymph nodes accumulated sufficient quantities of flint dust to produce obstructive lesions in this location and there were immature silicotic foci within the lungs themselves. These were apparently adequate to influence the behavior of the superimposed infection, although the differences between dusted and infection control animals were not as marked as might have been for the purposes of this experiment. Reaction to the inhaled flint accentuated the response to the more virulent parent

strain R1 microorganisms but had no effect upon those of the resistant dissociant colonies whose effect was greater in the silicotic than in the normal guinea pig.

In the normal animals not exposed to dust, the parent strain behaved typically. Macroscopic, caseous tubercles developed in the lungs and tracheobronchial lymph nodes with microscopic noncaseous foci in the spleens of about a quarter of them. After four months the pulmonary lesions had begun to heal and by the sixth month resolution had brought about a marked reduction in the number of subpleural tubercles. Complete healing with resolution of all the lesions would presumably have occurred as it regularly does within a period of eighteen to twenty-four months but the experiment was terminated at the sixth month. The successive stages of healing by resolution have been described previously (12).

The resistant dissociant in normal guinea pigs produced grossly visible pulmonary lesions in only occasional animals (4 to 14) and these changes were not typical tubercles. Reaction was limited to focal collections of monocyctic cells infiltrated with a small number of neutrophilic and eosinophilic polynuclear leucocytes. The extent of the lesion was rarely sufficient to obliterate included air spaces and thus produce a compact nodular tubercle. Caseation was detected in only one lesion of the entire series. With healing, which was well advanced by two and one-half months, there was only slight thickening of alveolar walls in a localized area due to the persistence of a limited number of monocyctic cells. Lymph node lesions were essentially the same as those in the lungs.

In silicotic guinea pigs, the parent strain manifested typical behavior, although as previously intimated the amount of silicosis was insufficient to permit maximal effects upon the infection within a period as short as six months after its administration. Both the number and the size of the tubercles in the silicotic animals were greater than in the undusted controls. Paradoxically there were more tubercles in the subgroup kept in a normal atmosphere after administration of infection than in the other subgroup that was returned to the dust house for six months. In the control series the average number of subpleural tubercles was approximately 8; in the dusted series infected and then kept in a normal air, 10; and in the series kept in dust both before and after infection, 16. However, unlike the controls, all animals exposed to dust developed not only subpleural lesions that could readily be counted but a variable number of lesions in the deeper portions of the lungs. The average diameter of the R1 tubercles in a normal guinea pig is about 1 mm., in silicotic guinea pigs it varies between 2 and 4 mm. In the control series, as previously indicated, the number of tubercles decreases at each successive sacrificing period; in dusted animals there is an increase.

In this experiment the actual numbers of subpleural tubercles counted in 5 undusted controls sacrificed at six months were 0, 1, 4, 7 and 9; in 5 animals infected after a six-month dust exposure and then returned to the dust house, 6, 15, 5, 5 and 6; and in 6 guinea pigs similarly exposed but kept in a normal atmosphere, 20, 25, 15, 25, 40 and 40. One member of the latter subgroup sacrificed eight weeks after infection had developed generalized chronic silico-tuberculosis

with pulmonary cavities and massive disease of the spleen and liver. If the experiment had been continued for another six months, experience leads us to believe that this result would have been attained in a majority of the long-term survivors. Progressive disease of this nature has been described elsewhere (6).

The *resistant dissociant* had no such effect in silicotic animals. Both grossly and microscopically the lesions were essentially indistinguishable from those in the nondusted controls. The localized areas of proliferation were perhaps at first somewhat larger and more compact than in the controls but there was no tendency to form true tubercles and no caseation was detected in any lesion. In successive sacrifices the reaction to infection was retrogressive rather than progressive.

*Effect of infection upon the silicosis:* As elsewhere described, the presence of typical R1 tuberculous infection tends to accelerate the development of the silicotic reaction, presumably because obstructive fibrosis in the tracheobronchial nodes interferes with lymphatic drainage from the lung. This was observed in the series where dust exposure was continued after infection with parent strain microorganisms. It did not appear in the group similarly infected with resistant dissociant bacilli, presumably because lymph node reaction was so insignificant.

*Tuberculin sensitivity:* Intracutaneous tuberculin tests were made upon all infected animals in this experiment on the eighteenth, forty-second and sixty-seventh days after infection. Those given the typical variant for the most part reacted on the first test and by the forty-second day strong reactions were elicited in all members of this group. Associated silicosis of the degree encountered in this or other similar experiments has no influence upon skin hypersensitiveness.

No animal infected with the resistant variant reacted on the eighteenth day; later the responses were generally weak. In the last test given on the sixty-seventh day after infection there was a well marked decrease in sensitivity and, in most of the animals in which slight or indeterminate reaction had been read previously, the tests were now frankly negative. In the subgroup of 28 exposed to dust, 3 animals showed a 2+ reaction, the rest with one exception were interpreted as  $\pm$  or negative. Surprisingly the degree of sensitiveness was appreciably higher in the controls than in silicotic animals. No correlation between tuberculin hypersensitivity and the severity of histological reaction could be established. The generally weak reactions produced by the inhalation of the avirulent dissociant is undoubtedly an expression of the small amount of foreign protein introduced into the lungs and, since proliferation of such organisms must be slight or absent, there is little subsequent increase. Previous tests upon animals infected with avirulent dissociants produced much higher skin hypersensitivity (13) but in all of them injection insured a primary implantation of a larger number of bacilli within the tissues.

#### CONCLUSIONS

1. Typical cultures of the R1 strain of *Mycobacterium tuberculosis* possess a low but considerable degree of virulence for normal guinea pigs. By inhalation they

provoke the formation of a single crop of primary caseous tubercles in the lungs and tracheobronchial lymph nodes with the development of a bacteremia and the establishment of abortive proliferative lesions in the spleens and livers of some of the animals. Subsequent healing by resolution is the rule. When inoculated directly into the brain they cause fatal disease of that organ.

2. Under artificial cultivation failure to maintain proper conditions for growth occasionally results in spontaneous dissociation of this organism with complete loss of virulence.

3. By a method described in this paper it is possible to produce at will avirulent dissociants of this strain which likewise possess no demonstrable virulence.

4. In normal guinea pigs inoculation of these avirulent dissociants produces slight transitory, noncaseous lesions and direct injection into the brain has a similar effect without apparent influence upon health.

5. The undissociated parent strain appears to retain a latent power of invasiveness which becomes manifest when the resistance of the host is lowered for any reason. Examples of such depression of host resistance occur with great rarity in occasional apparently normal guinea pigs; they are a regular feature of the silicotic host.

6. The resistant avirulent dissociants would appear to have lost this latent power of invasiveness for they have no more effect upon silicotic than upon normal guinea pigs.

7. The resistant or avirulent variant of the R1 strain is in all respects like corresponding variants of other strains which arise spontaneously under prolonged cultivation on artificial media.

8. It is possible that silicotic animals could be used to measure minor differences in virulence of colonies obtained during the dissociation of other strains of *Mycobacterium tuberculosis*.

#### CONCLUSIONES

1. Los típicos cultivos de la cepa R1 del *Mycobacterium tuberculosis* poseen una virulencia baja, pero considerable para los cobayos normales. Por inhalación provocan la formación de una sola cosecha de tubérculos caseosos primarios en los pulmones y ganglios linfáticos tráqueobronquiales, con formación de bacteriemia y establecimiento de lesiones proliferantes abortivas en el bazo e hígado de algunos de los animales. Por lo general sobreviene cicatrización por resolución. Inoculados directamente en el cerebro producen esos cultivos enfermedad letal de dicho órgano.

2. De no mantenerse condiciones adecuadas para el crecimiento en el cultivo artificial, puede sobrevenir a veces disociación espontánea del microbio, con pérdida absoluta de la virulencia.

3. Con un método descrito en este trabajo es posible producir, a voluntad, formas avirulentas de esta cepa, que tampoco poseen virulencia demostrable.

4. En los cobayos normales la inoculación de estas formas avirulentas produce lesiones no caseosas, leves, transitorias, y la inyección directa en el cerebro ejerce un efecto semejante sin influjo visible sobre la salud.

5. La cepa primitiva no disociada parece conservar una facultad invasora latente que se manifiesta cuando la resistencia del huésped se debilita por alguna razón. Ejemplos de tal disminución de la resistencia del huésped ocurren raramente en cobayos al parecer normales, pero constituyen un fenómeno corriente en el huésped silicótico.

6. La forma avirulenta resistente parece haber perdido esta facultad latente de invasión, pues no ejerce más efecto sobre los cobayos silicóticos que sobre los normales.

7. La variedad avirulenta o resistente de la cepa R1 es, en todos respectos, semejante a las variedades correspondientes de otras cepas que surgen espontáneamente bajo condiciones de cultivo prolongado en un medio artificial.

8. Quizás puedan utilizarse animales silicóticos para apreciar las diferencias menores en la virulencia de las colonias obtenidas durante la disociación de otras cepas del *Mycobacterium tuberculosis*.

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# HISTORY OF H37 STRAIN OF TUBERCLE BACILLUS<sup>1</sup>

W. STEENKEN, JR. AND L. U. GARDNER

The year 1945 marked the fortieth anniversary of the isolation of the Saranac Laboratory strain of the human type tubercle bacillus, H37. Unlike many microorganisms grown on artificial media for prolonged periods, this strain has retained much of its original virulence and is still capable of producing progressive, generalized tuberculosis in guinea pigs. Since it is widely used in many laboratories, a record of its life history should be of general interest.

To-day most of the large institutes and laboratories for tuberculosis research maintain H37 as one of their stock cultures for experimental and comparative virulence tests. It was one of the strains for the basic studies of the Research Committee of the National Tuberculosis Association. Anderson has used it extensively in his work on the chemistry of the tubercle bacillus; and upon its purified lipids, phosphatides, proteins and carbohydrates, Dr. Florence Sabin carried on her investigation of the tissue reactions to the components of the tubercle bacillus. H37 has been widely used for the production of tuberculin, living and heat-killed antigens for serological and immunological studies and as the virulent infecting organism for testing immunity in experimental tuberculosis. Feldman, Hinshaw and others besides ourselves have regularly used strain H37 for assaying in animals the effect of new chemical compounds that may have specific action in the treatment of tuberculosis. A committee of the National Tuberculosis Association has recommended its inclusion among a group of standard strains to be maintained for the use of experimenters in the field of chemotherapy.

The history of this strain begins in 1905 when Dr. Edward R. Baldwin recovered it from the sputum of a 19 year old male patient suffering from chronic pulmonary tuberculosis. The records show that the first culture was grown on a Hess agar plate enriched with cow's serum. The culture medium, Hess agar No. 2, had the following formula:

Agar.....	10 g
Heyden food.....	5 g
NaCl.....	5 g
Glycerin.....	30 cc.
5 cc. of 28.6 per cent of Na <sub>2</sub> CO <sub>3</sub> (crystals)	
Water.....	1,000 cc.

After the first generation the strain was transplanted onto various solid media enriched with either serum, meat extract or egg, on which it was maintained until 1917. At that time it was transferred to glycerol beef broth and glycerol agar. At the Saranac Laboratory the organism was continually subcultured every twenty days on both of these media, but in 1920 the Research and Clinical Laboratory at Trudeau Sanatorium established a collateral line upon Proskauer and Beck's synthetic fluid medium. Thus, for the first seventeen years of its exis-

<sup>1</sup> From the Research and Clinical Laboratory, Trudeau Foundation, Trudeau, New York.

tence strain H37 was maintained upon media heavily enriched with products of animal origin; then it was transferred to glycerol agar and broth and three years later a parallel series was started on a purely synthetic medium.

During the period from 1900 to 1912, Baldwin, Krause and Paterson were carrying out a host of pioneer experiments on infection and immunity in guinea pigs and rabbits. They regularly used strain H37 and their reports indicate that it was highly virulent for guinea pigs but only moderately so for rabbits, a behavior which marks it as distinctly human in type. Publication of many of these studies brought requests for subcultures of H37 and for years it was distributed to laboratories far and wide. Even mention of these and the subsequent Saranac Lake experiments with the strain is beyond the scope of this review; it is our purpose merely to discuss a few that bear upon fluctuation in its pathogenicity for animals.

Until 1922, H37 consistently maintained full virulence for guinea pigs and would produce generalized tuberculosis by any method of administration. In January of that year a large group of guinea pigs, infected by inhalation, showed massive disease of the lungs with extensive involvement of the spleen and lymph nodes when sacrificed two months later. However, in August of the same year another group, similarly infected, did not respond with the same uniformity; only a few of the animals developed progressive disease. Shortly thereafter an intraperitoneal injection of a massive dose failed to produce anything but localized tubercle. This experiment led to temporary abandonment of the strain for routine experiments in the Saranac Laboratory. However, in December, 1929 a group of guinea pigs that had been exposed to coal dust was given an inhalation infection with H37 and it was noted that the coal dust had not inhibited the growth of organisms nor prevented a retarded but definite development of chronic progressive tuberculosis in most of the animals. Again, in February of 1930 inhalation infection with H37 was administered to guinea pigs exposed to quartz dust and it was found that the silica caused the infection to progress rapidly in a majority of the animals; in a few cases most of the bacilli had apparently died before the silicosis could exert its usual stimulating effect. There was conclusive evidence of waning virulence not so complete but that silica could still stimulate growth. From 1930 until 1940 H37 was not used at all for virulent infection in the Saranac Laboratory and a succession of strains recently isolated from tuberculous patients was substituted. None of these strains was satisfactory because one after another they likewise lost virulence after a few years' growth upon glycerine beef broth, glycerine agar and Petroff egg medium.

During the period from 1922 to 1926 other laboratories which have maintained independent transplants of strain H37 likewise reported that their cultures were fluctuating in virulence and requests for fresh cultures were unusually numerous at that time.

The cause of this rather abrupt change in the behavior of a strain that had for some twenty-two years so consistently maintained a uniform degree of virulence not only in the Saranac Laboratory but in many others throughout the country was the subject of much speculation. Our culture media came under suspicion

for other more recently isolated strains were also losing virulence within a period of two or three years and another widely used Saranac Laboratory strain, R1, would no longer produce its usual self-limited caseous tubercle. The detailed record of this unique low virulent strain has been recounted elsewhere (1). A review of the situation indicated no apparent change in virulence of H37 during the five-year period immediately after it was transferred to glycerol media and deprived of serum or egg. The glycerol agar and broth were prepared by the same formula and method before and after the change. The only departure that could be discovered was the substitution of a new brand of peptone used in making the basic beef broth. Before World War I we had a large stock of imported Witte's peptone which was not exhausted until 1922. In that year we were forced to substitute an American product prepared by Fairchild. After sterilizing the broth made with this material a black precipitate would settle out of the fluid and this was removed by filtration through a Berkefeld filter. In so doing it is quite conceivable that we may have either removed essential nutrients from the broth or altered its concentration of salts. The latter we now realize is particularly likely to cause loss in virulence. We have always suspected that other laboratories, forced like ourselves to change their brand of peptone, may have produced similar alteration. Whatever the cause, there must have been some factor that operated widely to account for a rather sudden change in virulence of a previously stable microorganism, subcultures of which had been growing in so many different laboratories.

Fortunately for the future usefulness of strain H37 not all the eggs were in the Saranac Laboratory basket; collateral lines of this culture had also been established in the Research and Clinical Laboratory at Trudeau Sanatorium. There, transplants were maintained upon both glycerol broth and upon Proskauer and Beck's synthetic medium which contains no peptone. When the relative virulence of these two lines of H37 culture was tested it was found that the organisms grown on the synthetic medium were much more potent. From this line all subsequent transplants of virulent H37 have been made and Proskauer and Beck's medium is now our standard for the maintenance of stock cultures.

The mechanism by which strains of *M. tuberculosis* lose virulence under artificial cultivation probably involves a process of dissociation. Strain H37 was used in the early studies of this phenomenon at the Research and Clinical Laboratory. In 1927 Petroff and Steenken observed that the bacilli transplanted from glycerol broth produced two distinct forms of colony on egg plates. There were a few finely stippled, confluent colonies which would provoke progressive disease in guinea pigs. The predominating form of growth, however, was a rough, papilla-like conformation with a clear-cut periphery whose virulence was appreciably less marked. While organisms from such colonies would cause progressive tuberculosis, the rate at which disease developed was much slower. The colony of less virulence was subject to a process of further attenuation by continued growth on potato bile medium, which Calmette had already shown to be a favorable environment for this purpose. After many transfers the colony structure finally was stabilized as a sharply defined, worm-like formation composed of

smooth coils. Inoculation of bacilli from such colonies into guinea pigs produced only localized, nonprogressive lesions, but there was associated skin hypersensitivity to Old Tuberculin and a limited degree of resistance against reinfection with either the virulent dissociant of the parent strain or other virulent tubercle bacilli.

These experiments were later amplified in 1935 by another method of dissociation; strain H37 as well as other virulent organisms were plated on solid egg media of pH 6.2. The resulting cultures were allowed to age at 37°C. for three or four months, at the end of which time the original dry, discrete colonies had liquefied to be transformed into a confluent viscid mass. In the midst of this mass, new, raised, secondary, discrete colonies finally made their appearance. When the latter were picked and plated on fresh egg medium the resultant growth exhibited the same colony structure as that of the avirulent dissociant previously stabilized on potato bile. Tested in guinea pigs these organisms likewise exhibited almost no virulence.

Since the predominating colony in plate cultures of H37 and other strains previously grown for long periods on glycerol broth has the structure of an avirulent dissociant it would appear that continued transplantation on this medium may ultimately result in the persistence of nothing but such mutants. It is assumed that the glycerol beef media in use to-day favor the growth of such dissociants at the expense of the virulent forms. Whether the substitution of a new brand of peptone with resultant alteration in composition of the medium was responsible for the sudden loss of pathogenicity of H37 still remains a mystery. Pending further research to demonstrate the underlying principles, we elect to abide by empirical experience and rely upon Proskauer and Beck's synthetic medium for the maintenance of virulence of stock strains like H37.

#### SUMMARY

This strain of *M. tuberculosis* was isolated in the Saranac Laboratory forty years ago. Transplants have been used so widely throughout the United States in basic research like that of Anderson on the chemistry of the tubercle bacillus and of Sabin on its protein constituents that a detailed record of its life history is now being published. At times, transplants of this microorganism in different laboratories have undergone spontaneous dissociation with persistence of only avirulent mutants. Under proper conditions of cultivation, however, it is possible to maintain full virulence. The virulent dissociant will be among the strains carried by the Culture Depot of the National Tuberculosis Association for distribution to investigators in the fields of chemotherapy and other research.

#### SUMARIO

Esta cepa de *M. tuberculosis* se aisló en el Laboratorio de Saranac hace 40 años. En los Estados Unidos tanto se han empleado los trasplantes en investigación básica, por ejemplo, la de Anderson sobre la química del bacilo tuberculoso, y la de Sabin sobre sus componentes proteínicos, que actualmente se publica una

historia detallada de su vida biológica. A veces los subcultivos de este microorganismo en diferentes laboratorios han experimentado disociación espontánea, persistiendo únicamente las mutantes avirulentas. Sin embargo, en condiciones adecuadas de cultivo, es posible mantener plena virulencia. La disociante virulenta formará parte de las cepas que mantiene el Depósito de Cultivos de la Asociación Nacional contra la Tuberculosis para distribución a los investigadores en los campos quimioterapéutico y otros.

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## CULTURES OF PULMONARY SECRETIONS<sup>1,2</sup>

Their Accuracy in the Evaluation of Activity in Pulmonary Tuberculosis

L. L. SANFORD

In the hope of evaluating the relative efficiency of routine procedures used to demonstrate tubercle bacilli, all admissions to Muirdale Sanatorium for a five-year period, beginning January 1, 1940 and ending January 1, 1945, were reviewed. This group consisted of 2,252 patients: 126 children and 2,126 adults.

Routine laboratory methods in use throughout the period designated were as follows:

Specimens for laboratory examination were secured by (1) collection of the sputum as expectorated by the patient, (2) aspirations of the fasting stomach contents, and (3) bronchoscopic aspirations.

Pulmonary secretions thus obtained were examined for tubercle bacilli (1) by microscopic study of direct smears and concentrates, (2) by cultures and (3) by guinea pig inoculation. After the year 1941, guinea pig inoculations were rarely used, being reserved primarily for special studies.

### ADULT GROUP

Of the 2,126 adult patients, tubercle bacilli were demonstrated in 1,641 and not demonstrated in 411. Seventy-four patients considered to have had inadequate laboratory studies were not classified, since it was thought advisable to exclude patients who had not been studied by cultures or guinea pig inoculation.

*Positive group:* The admission period of study required to demonstrate tubercle bacilli varied from a few days to two and one-half or even three months.

Table 1 indicates the laboratory procedures used and the sources of the specimens. Four hundred eight patients were first found positive by culture. Hence, if cultures had not been used, 408 positive patients (29 per cent) would have been designated as negative on examination on admission. In other words, direct smears and concentrates failed in 29 per cent of the 1,641 positive adult patients during the admission period of study.

Speculation as to whether later examinations, after the admission period, yielded secretions more favorable to examination by direct smear or concentrate led to a review of the complete laboratory work accumulated during the patients' stay in the Sanatorium. It was found that direct smears and concentrates failed to demonstrate tubercle bacilli at any time in 273 of the 1,641 patients. Assuming these failures to be due either to the inefficiency of direct smears and concentrations or to the infrequency of their use, the latter possibility was investigated. It was found that a total of 4,652 examinations were done on these 273 patients as follows: examinations of sputa consisted of 20 direct smears,

<sup>1</sup> From the Muirdale Sanatorium, Wauwatosa, Wisconsin.

<sup>2</sup> Presented before the Mississippi Valley Trudeau Society on October 9, 1945 at Chicago, Illinois.

928 concentrates, 920 cultures and 12 guinea pig inoculations; examinations of gastric contents consisted of 1,291 concentrates, 1,278 cultures and 136 guinea pig inoculations; and examinations of specimens collected by bronchoscopic aspiration consisted of one direct smear, 33 concentrates and 33 cultures.

The paucity of direct smears in this group is referable to the judgment of the laboratory worker. Specimens were examined grossly and, if it appeared from such observation that a direct smear would not be fruitful, the specimen was concentrated before microscopic study.

The number of gastric specimens (1,291) is somewhat misleading. During the last year covered by this study nearly all such specimens consisted of five pooled aspirations.

If the implication from the above data that cultures are more accurate than smears is valid, cultures should then demonstrate tubercle bacilli better in the diagnostically more difficult patients, those with minimal pulmonary tuberculosis. A study of 105 patients—all those with minimal pulmonary lesion encountered in the positive group—revealed that 78 (70 per cent) were first found posi-

TABLE 1

*Methods used for the discovery of tubercle bacilli in the pulmonary secretions of 1,841 adults with active pulmonary tuberculosis*

METHOD OF EXAMINATION	SOURCE OF THE SPECIMEN			TOTAL
	Sputa	Gastric contents	Bronchoscopic aspirations	
Direct smear.....	923	0	0	923
Concentrate.....	229	65	2	296
Culture.....	250	154	4	408
Guinea pig inoculation.....	0	14	0	14

tive by culture. Thus, direct smears and concentrates failed to demonstrate tubercle bacilli in 70 per cent of the 105 positive patients with minimal pulmonary tuberculosis. In addition, a study of the complete sputum records of these 78 patients revealed that 55 were never positive by any method other than culture; 9 additional ones were positive by both culture and guinea pig inoculation but by no other method.

Further consideration of the positive group was made on the basis of mortality. The distribution of deaths in the Sanatorium as related to the methods used in discovering tubercle bacilli in the pulmonary secretions was analyzed. It was found that, of the 923 patients first positive by direct smear, 427 (46 per cent) died in the Sanatorium; of the 296 patients first positive by concentrate, 86 (28 per cent) died; of the 408 first positive by culture, 46 (11 per cent) died; and of the small group first positive by guinea pig inoculation, only 2 (14 per cent) died.

When the source of the specimen was considered, it was found that the highest mortality (46 per cent) was in the group first found positive by direct smear of

the sputum, while the lowest mortality (4 per cent) was in the group first found positive by culture of the gastric contents. If we assume mortality to be an index of the extent of the disease or the severity of the pathological process, it seems logical to believe that culture methods, as compared to smears and concentrates, are more capable of demonstrating tubercle bacilli in the less severe pathological processes.

*Negative group:* As previously stated, no patient was classified as negative unless one technically successful culture or one successful guinea pig inoculation was reported. This group consists of 408 patients with a variety of diseases. All had been admitted as tuberculosis patients or tuberculosis suspects. Many had a history of active pulmonary tuberculosis.

In 1928, Pinner and Werner (1) made a careful study of 37 adult patients who had been diagnosed as having pulmonary tuberculosis but "whose sputum had not shown any tubercle bacilli." These were the "negative" patients from a group of 507 with "active pulmonary tuberculosis." By smears, cultures and guinea pig inoculations, tubercle bacilli were found in 32 patients. But 5 patients (1.2 per cent of the 507) were thought to have active pulmonary tuberculosis despite the negative sputum studies.

We reviewed our negative patients to find possible active pulmonary tuberculosis which cultures had failed to indicate.

These patients were grouped as follows: nontuberculous pulmonary lesions, 173; no pulmonary lesions, 38; pleurisy with effusion, 19; pulmonary tuberculosis, 178.

Special attention was paid to the 178 patients with a diagnosis of pulmonary tuberculosis. Their chest roentgenograms were reviewed for evidence of active pulmonary tuberculosis. Sixteen patients with unstable lesions by serial roentgenological studies were found; 102 had stationary lesions; 60 had not received adequate roentgenological studies for classification. Here again special attention was paid to the 16 patients with unstable pulmonary lesions and with negative pulmonary secretions. It is to be emphasized that these 16 patients whose pulmonary secretions were negative by culture were in the Sanatorium for several months of observation. The longest period of sanatorium care was fourteen months, the shortest three months and the average eight months. Each patient had a positive tuberculin skin test. Eight showed some degree of toxemia for a period while in the Sanatorium. There were none whose blood showed eosinophilia. The chest lesions as visualized by roentgenograms varied in character but some degree of exudative disease was present. Fourteen were classified as minimal and two as moderately advanced. As noted above each had unstable pulmonary lesions as judged by serial roentgenograms. Fasting gastric contents were cultured for tubercle bacilli in each case and 8 were also studied by guinea pig inoculation. Sputum cultures were done when suitable specimens were raised. None of these laboratory studies demonstrated tubercle bacilli.

Thus we found a group of 16 patients (less than one per cent of the 1,657 active adult patients) with presumably active pulmonary tuberculosis in whom not only direct smears and concentrates but also cultures failed to demonstrate



tubercle bacilli. In other words, cultures were accurate in 99 per cent of our active adult patients.

#### EVALUATION OF PROCEDURES

In routine laboratory practice, all procedures relative to the examination of pulmonary secretions are not applied to all patients for obvious reasons.

In the composition of table 2, a failure of any given procedure was recorded when the procedure was either ineffective or not applicable. An attempt is made to show not only the inefficiency of single procedures but more particularly the advisability of using all current laboratory procedures when they can efficiently be applied.

TABLE 2

*The relative efficiency of methods used for the discovery of tubercle bacilli in the pulmonary secretions of 1,657 adults with active pulmonary tuberculosis*

PROCEDURES	EFFECTIVE IN	EFFICIENCY IN PER CENT
Direct smears.....	923 of 1,657 patients	55
Concentrates.....	1,368 of 1,657 patients	82
Cultures and guinea pig inoculations.....	1,641 of 1,657 patients	99

It was noted that 21 of our adult patients were found to have pleurisy with effusion but no visible parenchymal disease by roentgenological studies. The gastric contents of 2 (11 per cent) were positive by culture.

#### CHILDREN'S GROUP

This group consists of 126 children, varying in age from less than one year to 14 years, inclusive. All were admitted as tuberculosis suspects.

TABLE 3

*Methods used for the discovery of tubercle bacilli in the pulmonary secretions of 50 children with active primary tuberculosis*

METHOD OF EXAMINATION	SOURCE OF THE SPECIMEN			TOTAL
	Sputa	Gastric contents	Broncho-scopic aspirations	
Direct smear.....	3	0	0	3
Concentrate.....	0	2	2	4
Culture.....	2	19	1	22
Guinea pig inoculation.....	0	1	0	1

The manner of study was essentially the same as with the adult group. The problem of obtaining specimens from small children makes gastric aspiration almost a routine procedure. In the earlier period covered by this report, guinea pig inoculations were used more frequently than cultures.

Of the 126 children, tubercle bacilli were demonstrated in the pulmonary

secretions of 30 but not demonstrated in 95. One patient was excluded because of inadequate laboratory examinations.

*Positive group:* Tubercle bacilli were first demonstrated in these patients as recorded in table 3. This table shows that the pulmonary secretions of 22 patients (70 per cent) were first positive by culture. In later examinations, after the admission period, tubercle bacilli were never demonstrated in the pulmonary secretions of these 22 patients by direct smears or concentrates.

*Negative group:* Again a minimum of one technically successful culture or guinea pig inoculation was required for admission to the negative group. After exclusion of the nontuberculous patients and those with inadequate roentgenological studies, special attention was paid to the remaining 56 patients. Their chest roentgenograms were carefully reviewed.

It was found that 43 had stationary pulmonary lesions according to serial roentgenological studies and 13 had unstable lesions. The 13 children with unstable lesions, after an adequate period of observation, were thought to have active primary tuberculosis.

TABLE 4

*The relative efficiency of methods used for the discovery of tubercle bacilli in the pulmonary secretions of 43 children with active primary tuberculosis*

PROCEDURES	EFFECTIVE IN	EFFICIENCY IN PER CENT
Direct smears.....	3 of 43 patients	7
Concentrates.....	7 of 43 patients	16
Cultures and guinea pig inoculations.....	30 of 43 patients	69

The longest period of sanatorium care was seventeen months, the shortest three months and the average ten months. Each patient had a positive tuberculin skin test and 8 showed some evidence of persistent toxemia for a period while in the Sanatorium. The chest lesions as visualized by roentgenograms varied in character, 12 having some degree of exudative disease in the parenchyma. One had no visible parenchymal disease but moderate irregular bulging of the mediastinum. As noted above, each had unstable lesions by serial roentgenograms. Fasting gastric contents were cultured for tubercle bacilli in each case and 9 were also studied by guinea pig inoculation. Three had cultures of specimens obtained by bronchoscopic aspiration. These laboratory procedures did not demonstrate tubercle bacilli.

Thus the total number of children considered to have active primary tuberculosis was 43; 30 by demonstration of tubercle bacilli and 13 by clinical observation.

Table 4 is an attempt, as with the adult group, to evaluate the efficiency of the laboratory procedures used to demonstrate tubercle bacilli in the children's group.

Before concluding, it is significant to mention that 7 children had pleurisy with effusion with no visible pulmonary infiltration; 2 of these (28 per cent) had

positive pulmonary secretions as demonstrated by culture of their gastric contents.

#### SUMMARY AND CONCLUSIONS

In a review of 2,252 consecutive admissions over a five-year period the efficiency of direct smears and concentrates in comparison with cultures in demonstrating tubercle bacilli in pulmonary secretions is evaluated. The adequacy of the methods used in the discovery of tubercle bacilli in routine examinations is as follows:

1. *Adults*: Direct smears were effective in demonstrating tubercle bacilli in 55 per cent of 1,657 patients with active pulmonary tuberculosis. When concentrates were also used, 82 per cent of the same group were found positive. The use of cultures (with a small number of guinea pig inoculations), in addition to smears and concentrates, demonstrated tubercle bacilli in 99 per cent of these patients.

2. *Children*: Direct smears were effective in demonstrating tubercle bacilli in 7 per cent of 43 children with active primary tuberculosis; when smears of concentrates were also used, 16 per cent of the same group were found positive. The additional use of cultures made it possible to discover tubercle bacilli in 69 per cent of these children.

3. *Minimal pulmonary tuberculosis*: With the aid of cultures, tubercle bacilli were found in the pulmonary secretions of 86 per cent of 105 patients with active minimal pulmonary tuberculosis.

4. *Pleurisy with effusion*: In a series of 28 patients, both children and adults, with pleurisy with effusion and without roentgenologically demonstrable parenchymal disease, the pulmonary secretions of 4 (14 per cent) were positive by culture.

5. Deaths in the Sanatorium were almost twelve times (46 per cent as compared with 4 per cent) as frequent in patients first found positive by direct smear of their sputa as those first found positive by culture of their gastric contents.

#### SUMARIO Y CONCLUSIONES

En un estudio de 2,252 ingresos consecutivos durante un período de cinco años, se avalúa la eficacia de los frotos directos y los concentrados, comparados con los cultivos para el hallazgo del bacilo tuberculoso en las secreciones pulmonares.

1. *Adultos*: Los frotos directos resultaron eficaces para descubrir el bacilo tuberculoso en 55% de 1,657 enfermos con tuberculosis pulmonary activa. Cuando se emplearon también esputos concentrados, 82% del mismo grupo resultaron positivos. El empleo de cultivos (con un pequeño número de inoculaciones en cobayos), además de los frotos y concentraciones, demostró la presencia del bacilo tuberculoso en 99% de esos enfermos.

2. *Niños*: Los frotos directos sirvieron para demostrar la presencia del bacilo tuberculoso en 7% de 43 niños con tuberculosis primaria activa; al emplear también frotos de esputos concentrados, 16% del mismo grupo resultaron posi-

tivos. El empleo adicional de cultivos permitió descubrir el bacilo tuberculoso en 69% de dichos niños.

3. *Tuberculosis pulmonar mínima*: Mediante el empleo de cultivos se descubrieron bacilos tuberculosos en las secreciones pulmonares de 86% de 105 enfermos con tuberculosis pulmonar mínima activa.

4. *Pleuresía con derrame*: En una serie de 28 enfermos, tanto niños como adultos, con pleuresía con derrame y sin enfermedad parenquimatosa demostrable roentgenológicamente, las secreciones pulmonares de 4 (14%) resultaron positivas por cultivo, mientras que ninguna resultó positiva por frote directo o concentrado.

5. Las muertes en el sanatorio fueron casi doce veces (46% comparadas con 4%) más frecuentes en los enfermos que resultaron positivos primeramente por frote directo del esputo, que en los que resultaron primeramente positivos por cultivo del contenido gástrico.

Counsel and supervision by Dr. J. D. Steele and Dr. A. V. Cadden in the preparation of this report is gratefully acknowledged.

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## PLASMA AND URINARY ASCORBIC ACID IN TUBERCULOUS PATIENTS<sup>1,2</sup>

ELIZABETH V. WEBB, CLARA A. STORVICK AND KENNETH B. OLSON

Vitamin C therapy in pulmonary tuberculosis is often recommended and commonly applied, but there is considerable disagreement on the actual value of such treatment and a rather wide variation in the data concerning ascorbic acid metabolism in this disease. Tuberculosis is often said to be associated with lowered ascorbic acid values in blood plasma and urine even after administration of test doses (1 to 13). A number of authors, moreover, observe a parallelism between the degree of hypovitaminosis C and the extent and severity of the tuberculosis (4 to 8, 13 to 16). In contradiction, others (9, 12) find no correlation between ascorbic acid excretion and clinical condition.

Recently a daily supplement of 100 mg. ascorbic acid has been inaugurated at Firland Sanatorium, and one of the objectives of this study was to obtain some information as to whether this amount was adequate or in unnecessary excess. Since no observations on day-to-day values of urinary excretion or plasma ascorbic acid values in tuberculosis have been reported, the investigation of vitamin C nutrition of patients at this Sanatorium was begun with this type of study.

Marked day-to-day variations in urinary and plasma ascorbic acid values in the same subject on controlled ascorbic acid intake have been observed in normal adults (17). Because of the daily fluctuations, weekly averages of these values are considered a better indication of the vitamin C status of the individual than single determinations (18).

### METHODS

Daily plasma and urine values, and responses to test doses were determined on three groups of subjects. Each group consisted of 2 patients and one control. For the determination of plasma ascorbic acid, 2 cc. of blood were drawn by venipuncture into a dry syringe. The needle was removed and the blood carefully transferred, to avoid hemolysis, into small vials containing sodium oxalate (18). Plasma ascorbic acid was then determined by the method of Farmer and Abt (19). The titrations were completed as soon as possible after taking the samples to avoid loss of ascorbic acid (18). Most of the titrations were completed within two and a half hours; the maximum time to elapse between collection and titration of blood plasma was four hours.

Determinations of urinary ascorbic acid were made on twenty-four-hour specimens. With each voiding, 10 per cent by volume of 2 per cent metaphosphoric acid in 2N sulfuric acid was added as a preservative. The collections were kept in stoppered brown

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<sup>1</sup> From the Department of Home Economics, University of Washington, Seattle, Washington and Firland Sanatorium (City of Seattle Health Department), Richmond Highlands, Washington.

<sup>2</sup> The data in this paper are taken from a thesis presented by Elizabeth V. Webb to the Graduate School of the University of Washington in partial fulfillment of the requirement for the Master of Science degree, October, 1945.

bottles in a cool place. Ascorbic acid determinations, by titration with 2,6-dichlorobenzenoneindophenol dye, were made within three and a half hours after the last collection on aliquots of the pooled preserved urine specimens.

## DAILY STUDIES

Six patients on whom daily studies were done all had far advanced pulmonary tuberculosis. *I. C.* also had laryngeal and intestinal tuberculosis later, confirmed at postmortem examination. *H. G.* had laryngeal tuberculosis. *I. C.* and *H. G.* were febrile, the others afebrile. *K. H.* died two days after the two-

TABLE 1

*Ascorbic acid intake during experimental periods*

SUBJECT	NUMBER OF DAYS ON EXPERIMENT	AVERAGE ESTI- MATED DIETARY INTAKE, MG. ASCORBIC ACID	DAILY SUPPLE- MENT, MG. ASCORBIC ACID	AVERAGE TOTAL DAILY INTAKE, MG. ASCORBIC ACID
<i>H. G.</i> .....	7	90	100	190
<i>I. C.</i> .....	7	34	100	134
<i>E. S.*</i> .....	7	86	0	86
<i>E. H.</i> .....	14	91	0 200	91 (a) 291 (b)
<i>K. H.</i> .....	14	41	0 200	41 (a) 241 (b)
<i>J. T.*</i> .....	15	76	0 200	76 (a) 276 (b)
<i>V. J.</i> .....	8	151	0	151
<i>M. B.</i> .....	8	185	0	185
<i>E. B.*</i> .....	9	76	0	76

\* Control subject.

(a) First week

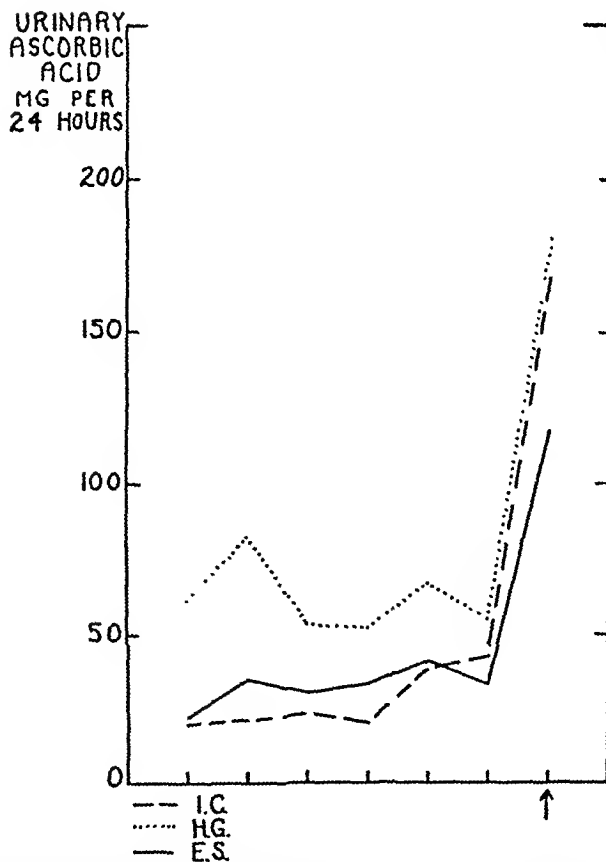
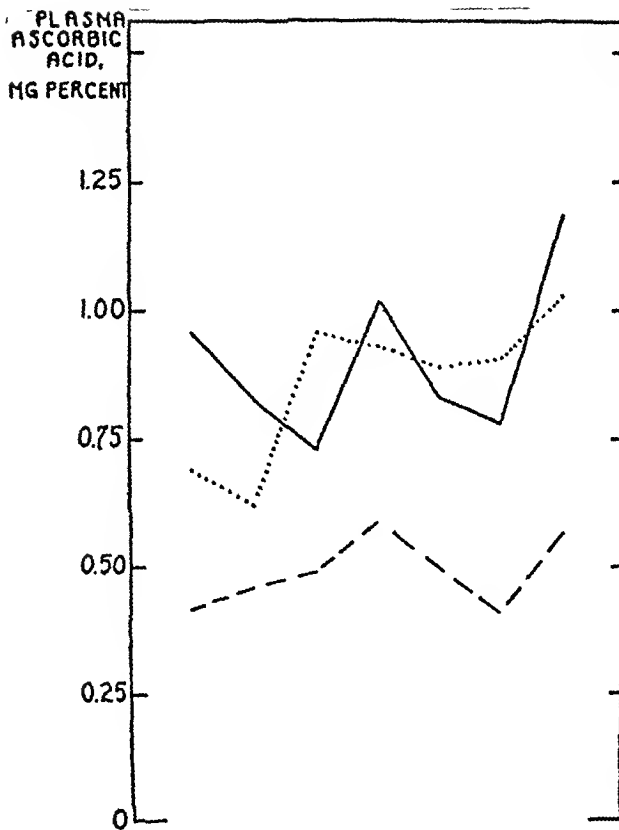
(b) Second week.

Note: The results of the studies on the three groups of patients are summarized in graphs 1, 2 and 3.

week study and *I. C.* two months after the test. At the time of the experiments, the condition of *H. G.*, *I. C.* and *K. H.* was considered worse, that of *E. H.* unchanged, and that of *V. J.* and *M. B.* improved, as compared with the condition on entry. Three normal controls were studied for the purpose of comparison. Although control subject *E. S.* became a patient ten weeks later, he was considered nontuberculous at the time.

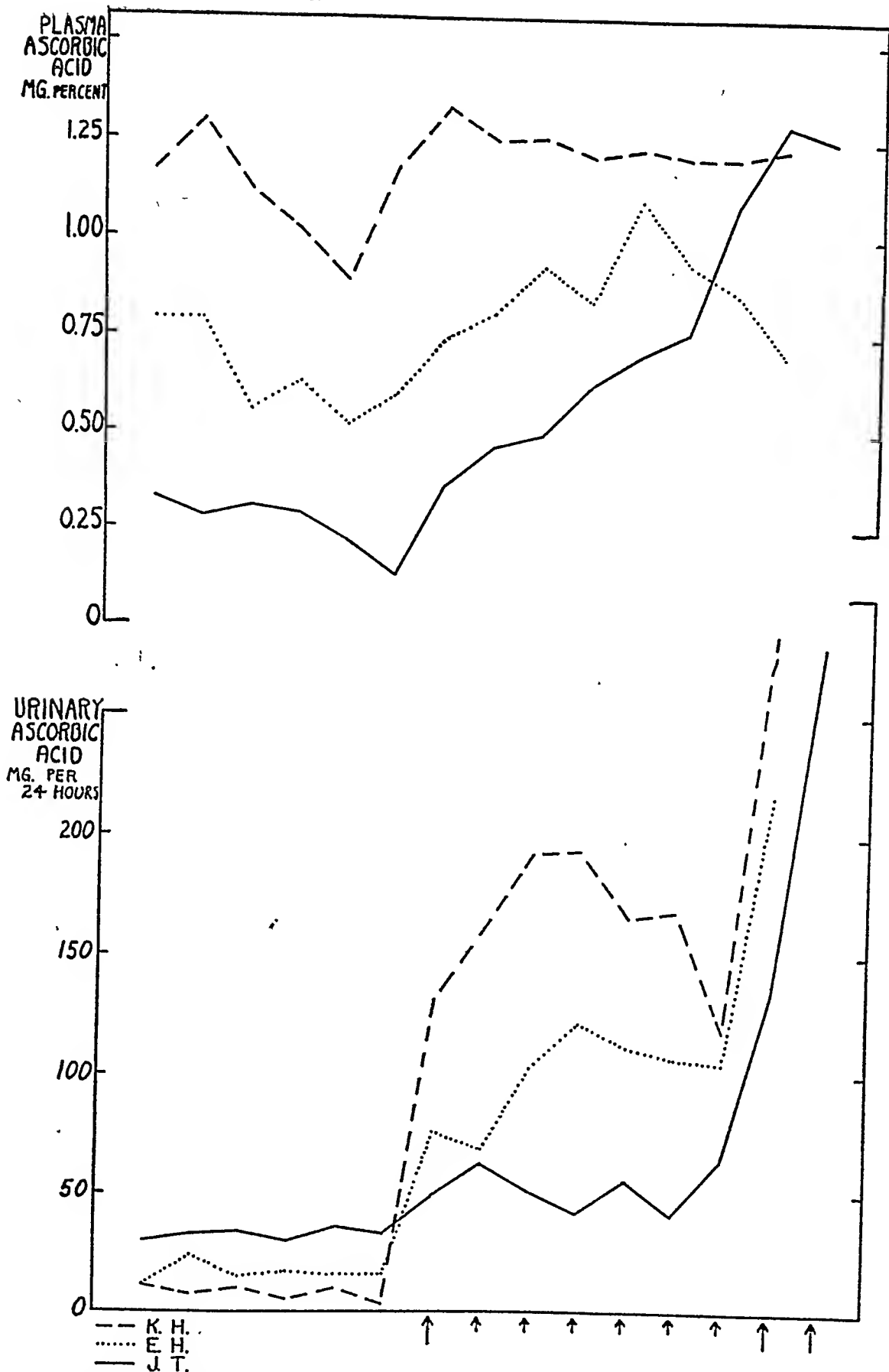
The ascorbic acid content of the food consumed by the subjects was estimated, using data in *Vitamin Values of Foods*, Miscellaneous Publication No. 505, U. S. Department of Agriculture, and is shown in table 1.

The results of the studies on the three groups are summarized in graphs 1, 2 and 3.



GRAPH 1. Daily twenty-four-hour urinary ascorbic acid outputs and plasma ascorbic acid values of subjects *I. C.*, *H. G.* and *E. S.*

Arrow indicates the administration of 400 mg. ascorbic acid as test dose.



GRAPH 2. Twenty-four-hour urinary ascorbic outputs and plasma ascorbic acid values of subjects K. H., E. H. and J. T.

Long arrows indicate the administration of 400 mg. and the short arrows 200 mg. ascorbic acid.



PLASMA  
ASCORBIC  
ACID,  
MG PERCENT

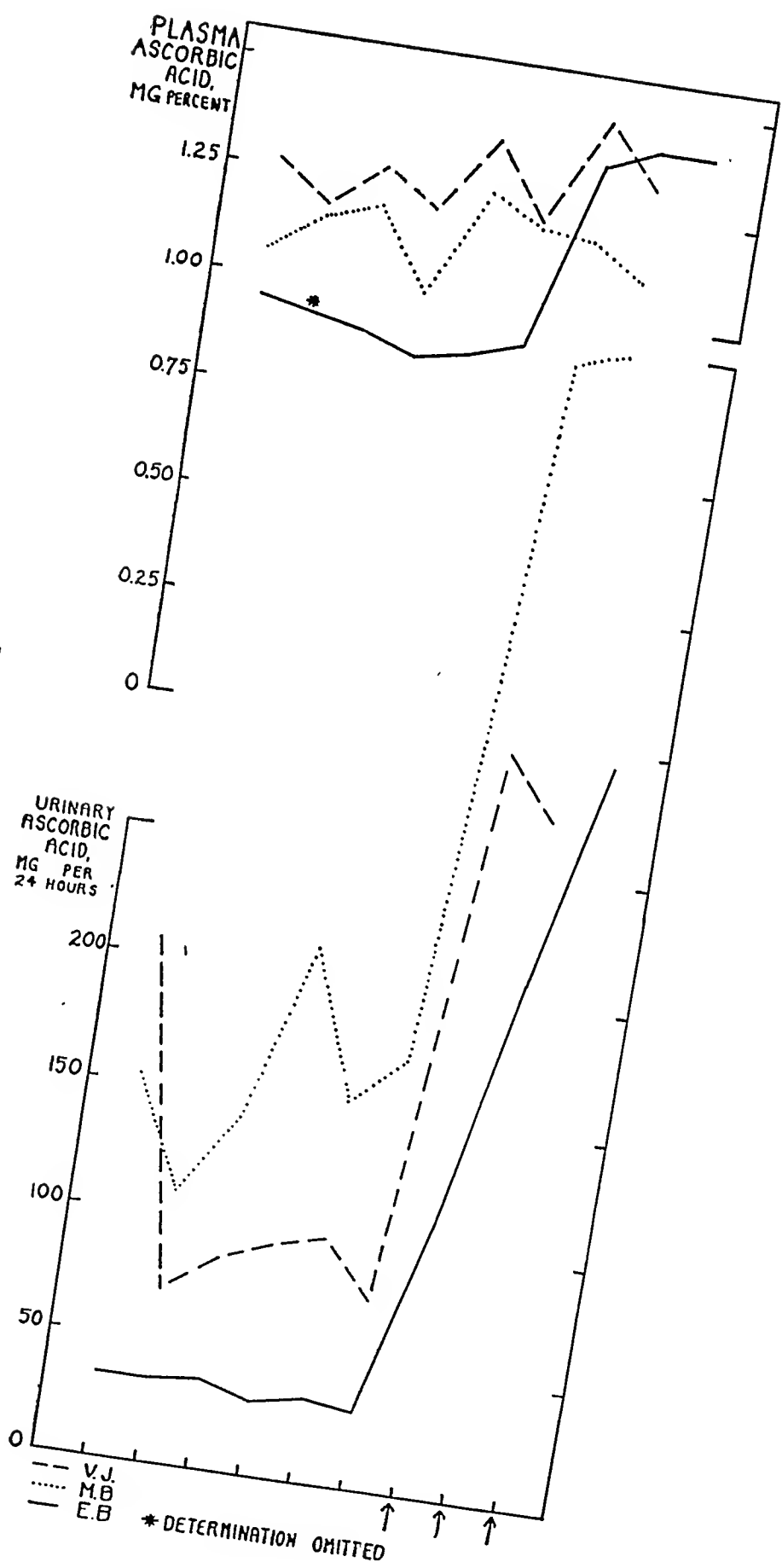
1.25  
1.00  
0.75  
0.50  
0.25  
0

URINARY  
ASCORBIC  
ACID,  
MG PER  
24 HOURS

200  
150  
100  
50  
0

-- V.J.  
... M.B.  
— E.B.

\* DETERMINATION OMITTED



## DISCUSSION

The first seven days of all three studies are comparable, except for the 100 mg. daily ascorbic acid supplement for *I. C.* and *H. G.* during the six days preliminary to the 400 mg. test dose. If daily values for all 9 subjects are compared, the urinary outputs seem to fall into three groups: (a) patients *V. J.*, *M. B.* and *H. G.* with high daily ascorbic acid excretion and response to test dose; (b) controls *E. S.*, *J. T.* and *E. B.* whose daily excretions of ascorbic acid are remarkably constant and similar, and within "normal" range; (c) patients *I. C.*, *E. H.* and *K. H.* with low daily ascorbic acid excretions. Of these, only *K. H.*, with a mean of 8 mg. per twenty-four hours, was excreting below reported normal resting levels of 13 to 15 mg. per day on adequate intake (20, 21). However, indicative of saturation (22), her response to the test dose was quite high, and repeated doses of 200 mg. ascorbic acid per day were followed by marked excretions of the vitamin.

The apparent depletion suggested by the low mean plasma concentration of *J. T.* during the first week may be attributed to a cold before and during this week and to the diet low in ascorbic acid which he is accustomed to eating.

These results on 6 patients do not substantiate the reports by other workers of lowered ascorbic acid excretions in tuberculosis (4 to 9, 12, 13, 23). Plasma ascorbic acid levels of the 9 subjects also do not suggest lowered values in tuberculosis. Four of the 6 patients had plasma ascorbic acid levels within the normal range of 0.7 to 1.5 mg. per cent (24), although *I. C.* with 0.48 was just above the normal lower limit of 0.4 mg. per cent (25). Furthermore, it may be noted that, while *I. C.* had a low plasma ascorbic acid value, her excretion of the vitamin was well within reported normal limits. On the other hand, *K. H.*, with low mean ascorbic acid excretion, had plasma values within the "optimal" range of normal. This would suggest that it is desirable to base conclusions concerning any person neither on plasma nor urinary values alone, but rather on a study of the complete plasma-urine-test-dose picture. The fact that all of the patients, including *I. C.* with intestinal involvement, excreted large quantities of ascorbic acid following ingestion of a test dose indicates that there was no failure to absorb the vitamin. It would have been of interest during the course of this experiment to compare the renal thresholds for ascorbic acid of *I. C.* and *K. H.* to ascertain whether this was a determining factor which would account for the discrepancy in the plasma concentrations of these 2 patients. It was felt that they were too critically ill to be subjected to hourly blood sampling following a large dose of ascorbic acid. An alternative might have been to measure the plasma ascorbic acid concentration before and perhaps two hours after a test dose of ascorbic acid.

## PLASMA ASCORBIC ACID DETERMINATIONS

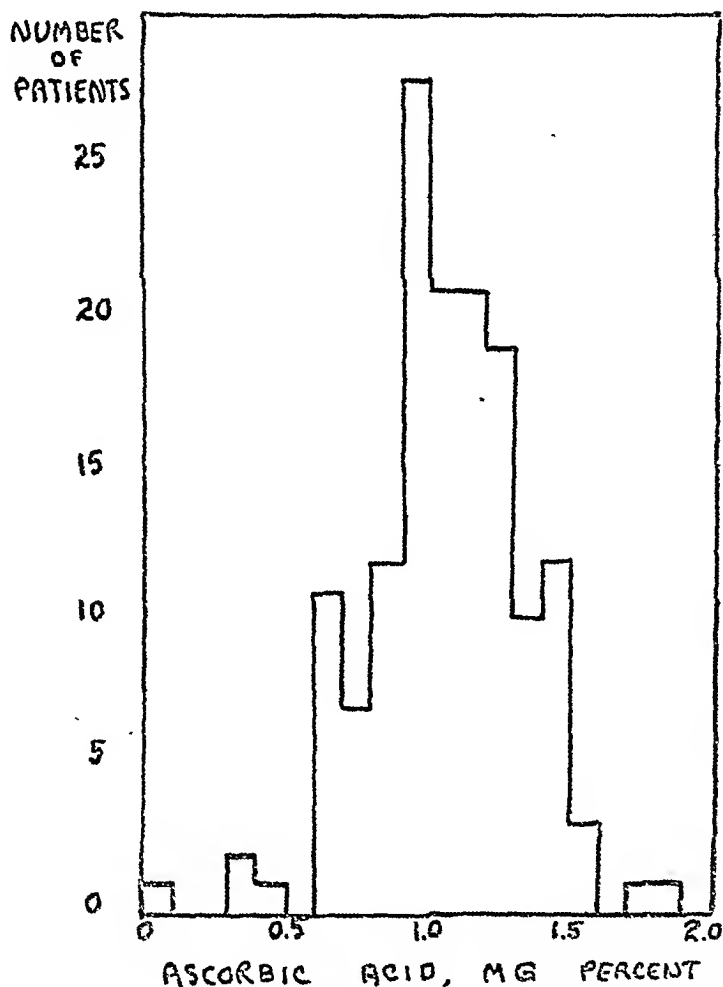
Inasmuch as the plasma and urine ascorbic acid values of the 6 patients in the foregoing studies were not as low as found by many investigators, single fasting plasma ascorbic acid values were determined in 150 tuberculous patients. This study was initiated in order to determine the general picture of plasma ascorbic

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GRAPH 3. Daily twenty-four-hour urinary ascorbic acid outputs and plasma ascorbic acid values of subjects *V. J.*, *M. B.* and *E. B.*

Arrows indicate the administration of 400 mg. ascorbic acid as test doses.

acid levels in patients with tuberculosis of varying degrees of severity and to ascertain whether the ascorbic acid provided at Firland Sanatorium by diet and supplementation was adequate for maintaining an optimal state of nutrition with respect to this vitamin. Although the mean value of a series of determinations is of greater significance (18), single fasting plasma ascorbic acid values reflect



GRAPH 4. Distribution of fasting plasma ascorbic acid concentrations of 150 tuberculous patients.

dietary intake and body stores of the vitamin without showing sharp fluctuations resulting from very recent ingestion of ascorbic acid (26).

The distribution of the fasting plasma ascorbic acid concentrations of the 150 patients is shown in graph 4. The values range from 0.09 to 1.84 mg. per cent, with a mean of 1.06 mg. per cent ascorbic acid. It was found that 94 per cent of the values lie between 0.6 and 1.5 mg. per cent; 90 per cent are over 0.7 mg. per cent, a value commonly accepted as normal (24). Plasma ascorbic acid levels

above 1.0 mg. per cent appear optimal in normal persons (27); 59 per cent of the patients in this survey had plasma ascorbic acid values above this concentration.

The 150 patients were classified according to the degree of tuberculosis as follows: 87, far advanced; 58, moderately advanced; 5, minimal tuberculosis. The mean plasma ascorbic acid value of those with far advanced disease was 1.03 mg. per cent. Moderately advanced cases showed a mean of 1.11 mg. per cent ascorbic acid and the mean of the minimal cases was 1.07 mg. per cent.

Fever as a result of tuberculosis has been mentioned as a possible factor increasing metabolic demands for ascorbic acid in tuberculosis (28, 29). Of the patients in this study, 13 of those classified as having far advanced tuberculosis were febrile. The mean plasma ascorbic acid concentration of these 13 cases was 0.82 mg. per cent, somewhat lower than the mean of 1.03 mg. per cent for the whole group with far advanced tuberculosis, but still within "normal" limits. It is also noteworthy that, while the lowest plasma ascorbic acid value in the study (0.09 mg. per cent) was that of a febrile patient, another febrile patient had the relatively high concentration of 1.44 mg. per cent.

#### COMMENT

This study would indicate, then, that 100 mg. of ascorbic acid daily, supplementing the hospital diet planned for a high ascorbic acid content, maintained the vitamin C nutrition of most of these tuberculous patients at a normal, and in some cases at an optimal level. These plasma values are higher than those reported by most writers (1, 4, 6, 8 to 10, 12, 13). The difference may be attributed in part to the high intake of ascorbic acid through diet and supplementation, in accord with the observations of other workers (3, 7, 14).

#### SUMMARY

1. Six-day means of plasma ascorbic acid levels and twenty-four hour urinary outputs and responses to 400 mg. test doses of ascorbic acid in 6 tuberculous patients and 3 control subjects did not indicate significantly lowered vitamin C nutrition in tuberculosis as reflected by plasma ascorbic acid levels or urinary output.

2. A marked discrepancy between plasma ascorbic acid values and twenty-four hour urinary excretion levels was found in the same patients. This indicates that neither test in itself is sufficient for establishing so-called saturation criteria. It would be desirable to determine the urinary excretion and plasma concentration as well as renal threshold for ascorbic acid before attempting to set normal values.

3. Single fasting plasma ascorbic acid concentrations of 150 tuberculous patients ranged from 0.09 to 1.84 mg. per cent, with a mean of 1.06 mg. per cent. If 0.7 mg. per cent is taken as the lower limit of normal, 90 per cent of the patients had normal plasma ascorbic acid values after two months of ascorbic acid supplementation. No correlation was noted between the degree or extent of tuberculosis and the plasma ascorbic acid concentrations.

## SUMARIO

1. En seis tuberculosos y tres testigos los promedios de seis días de niveles de ácido ascórbico en el plasma, y la excreción urinaria en 24 horas y la respuesta a dosis de prueba de 400 mg. de ácido ascórbico, no indicaron mayor disminución de la vitamina C en la tuberculosis, en lo que la reflejan el tenor de ácido ascórbico en el plasma o la excreción urinaria.

2. Los mismos enfermos mostraron marcada discrepancia entre los valores del ácido ascórbico en el plasma y en la excreción urinaria de 24 horas, lo que indica que ninguna de las dos pruebas basta para establecer los llamados criterios de saturación. Sería de desear que se determinaran la excreción urinaria y la concentración del plasma así como el límite renal para el ácido ascórbico, antes de tratar de establecer valores normales.

3. En 150 tuberculosos las concentraciones de ácido ascórbico en una sola muestra de plasma en ayunas variaron de 0.09 a 1.84 mg. por ciento con un promedio de 1.06 mg. Si se toman 0.7 mg. por ciento como el mínimo normal, el 90% de los enfermos poseían valores normales de ácido ascórbico en el plasma después de dos meses de administrárseles ácido ascórbico. No se observó relación alguna entre el grado o extensión de la tuberculosis y las concentraciones de ácido ascórbico en el plasma.

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# EFFECTS OF INTRANASAL INOCULATION WITH TUBERCLE BACILLI ON VITAMIN A STORES AND TISSUES OF MICE AND RATS<sup>1,2</sup>

A. B. McCOORD, C. P. KATSAMPES AND S. W. CLAUSEN

Previous work in our laboratory has shown that patients suffering from tuberculosis, particularly of the intestinal tract, have abnormally low concentrations of vitamin A and of carotene or provitamin A in their serum (1). When these patients are given a large amount of vitamin A by mouth, they do not absorb it nearly as well as do normal persons.

We thought it would be of interest to continue our studies with tuberculosis using experimental animals as subjects. In our work with tuberculosis, mice and rats were used as subjects. We used the intranasal method of inoculation which has proved so useful in the studies with murine pertussis being carried on in our laboratories (2).

The vitamin A in the tissues was determined as has been reported previously (3).

## INTRANASAL INOCULATION OF MICE WITH HUMAN TUBERCLE BACILLI

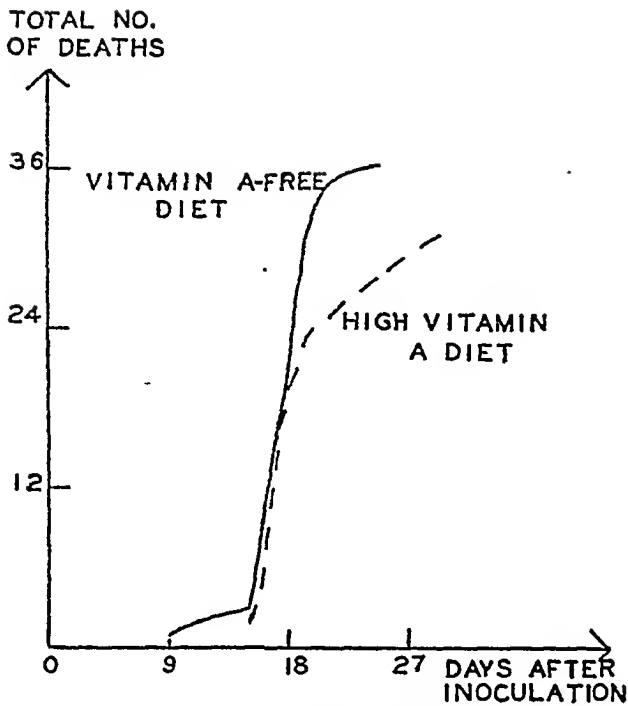
In the present mouse experiments, 110 male and 110 female, three-week-old mice were used. Since the mothers had received the same stock diet, it was assumed that the vitamin A stores of the young were approximately uniform. Ten male and 10 female mice were killed with illuminating gas and the amount of vitamin A in their livers and lungs was determined. The livers or lungs of 5 male or female mice were pooled for each analysis.

Fifty male and 50 female mice were lightly anesthetized with a mixture of one part chloroform and two parts ether, and 0.05 ml. of a heavy suspension of virulent human tubercle bacilli in 0.9 per cent sterile sodium chloride solution was introduced into their noses by means of a tuberculin syringe provided with a short, blunt needle. The tubercle bacilli used in making the suspension were not weighed. The remaining mice were kept as controls. The mice were kept in gallon glass pickle-jars containing a little paper bedding. The jars were closed with the metal covers in which holes were made to admit air and a drinking tube. Since 5 mice were kept in each jar, it is possible that they continued to inoculate each other. Fifty control mice and 50 inoculated mice received their usual diet of Purina dog chow and whole oats (high vitamin A diet), and 50 inoculated mice received Steenbock's vitamin A-free diet. Each group contained an equal number of males and females.

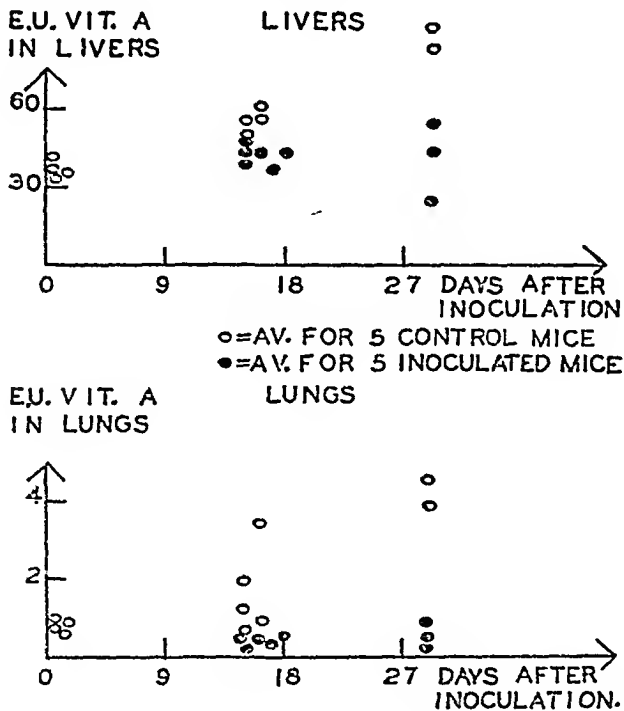
The inoculated animals began to die within nine days, and within thirty days most of them had died, as is shown in graph 1. The mice which received the high vitamin A diet lived somewhat longer than those which received the vitamin A-

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<sup>2</sup> A preliminary report of this work was given before the Division of Biological Chemistry at the American Chemical Society Meeting, New York City, September 12, 1944.



GRAPH 1. Survival of mice after intranasal inoculation with tubercle bacilli.



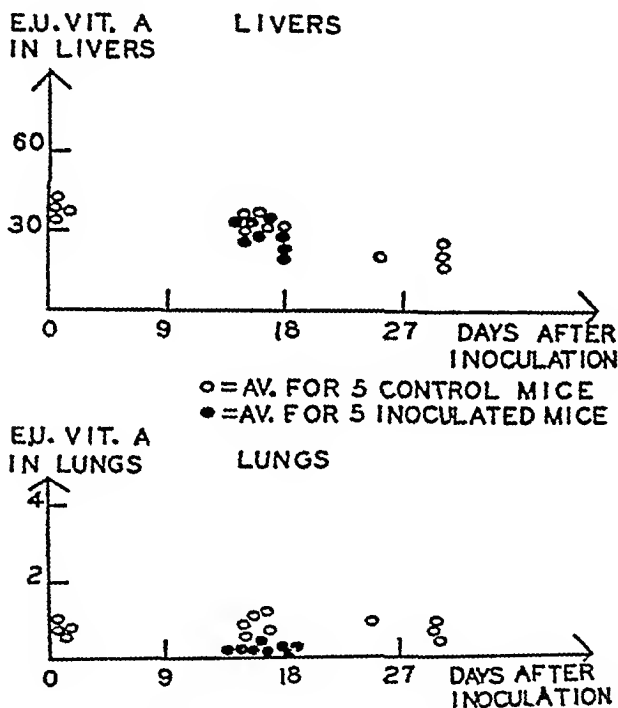
GRAPH 2. Vitamin A in livers and lungs of mice inoculated with tubercle bacilli. High vitamin A diet.



free diet. The control mice were killed at approximately the same time the inoculated mice died. On the thirtieth day all surviving animals were killed.

The lungs of the inoculated mice were much enlarged and contained a large amount of fat. The average weight of the control lungs was 0.157 g., and of the inoculated lungs, 0.543 g. Acid-fast bacilli were present in smears prepared from the latter lungs. The autopsies indicated that the involvement had remained localized in the lungs.

Graph 2 shows the amount of vitamin A in the livers and lungs of the mice which received the high vitamin A diet. The open circles represent average



GRAPH 3. Vitamin A in livers and lungs of mice inoculated with tubercle bacilli. Vitamin A-free diet.

values for 5 control mice, and the black circles, average values for 5 inoculated mice. One E. U. (Evelyn Unit) equals about 3.8 International Units of vitamin A. The amount of vitamin A in the livers and lungs of the control mice steadily increased as the animals grew and continued to ingest the high vitamin A diet. The amount of vitamin A in the livers and lungs of the inoculated group did not increase during the experiment. This was presumably due to lowered food intake and to the destructive effect of the reaction due to the inoculation.

Graph 3 shows the amount of vitamin A in the livers and lungs of the mice which received the vitamin A-free diet. The inoculation with tubercle bacilli did not appear to decrease the vitamin A of the livers but did decrease that of the lungs. In these experiments, the female mice usually had larger stores of vitamin

A than the males. This relationship has been observed in other species, including man.

#### INTRANASAL INOCULATION OF RATS WITH TUBERCLE BACILLI

In these studies, 100 three-week-old rats, which had received the same amount of vitamin A since birth, were placed on Steenbock's vitamin A-free diet. Four groups of 10 rats each were inoculated intranasally with 0.01, 0.1, 1 and 10 mg. (wet weight), respectively, of virulent human tubercle bacilli. In each case, the bacilli were suspended in 0.05 ml. of sterile 0.9 per cent sodium chloride solution. An equal number of uninoculated rats and a group of 20 rats given suspensions of

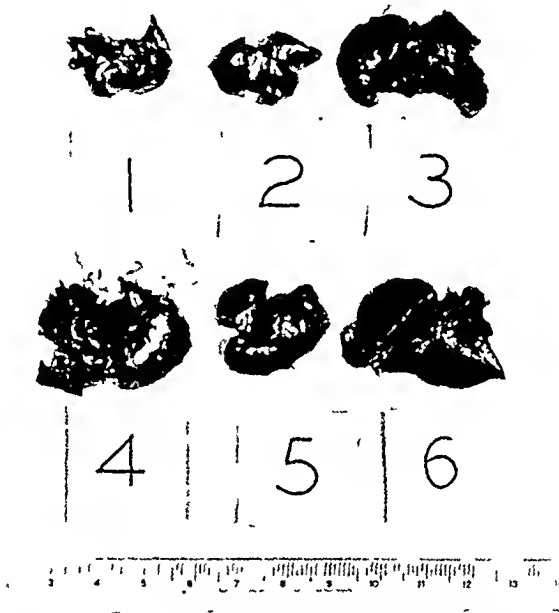


FIG. 1. Nos. 1 and 2 are lungs of control rats, and nos. 3, 4, 5 and 6 are lungs of rats which received, respectively, 0.01, 0.1, 1 and 10 mg. of tubercle bacilli.

killed organisms intranasally served as controls. The rats were housed in the same manner as the mice, except that 2 rats were kept in each jar. The survivors were killed eighty-three days after the inoculation. The average weight of the livers of the control group was 8.83 g., and that of the other group, 5.23 g. While the animals were not weighed, it was noted that those in the inoculated group were smaller.

The lungs of many of the inoculated rats were much larger and firmer than those of the control rats, as is shown in figure 1, in which nos. 1 and 2 are lungs of the control rats, while nos. 3, 4, 5 and 6 are lungs of rats which received, respectively, 0.01, 0.1, 1 and 10 mg. of tubercle bacilli. Nodular areas are evident on the surface of the lungs.

Acid-fast organisms were present in the smears prepared from these lungs. Guinea pigs injected with suspensions prepared from these lungs died. Lesions

characteristic of tuberculosis were found at autopsy of the guinea pigs, and acid-fast organisms were seen in smears taken from their tissues.

In the rats given suspensions of killed tubercle bacilli intranasally, the lungs were generally normal with occasional slight pneumonia not comparable to that of the experimental rats. None of the rats tested became tuberculin-positive to 10 mg. tuberculin.

Figure 2 shows a microscopic section of one of the inoculated lungs. Although tubercles characteristic of human tuberculosis are not found, and lipid-filled cells are prominent, the lesions indicate a reaction to viable if not multiplying tubercle bacilli. Some of the lungs show extensive granulomatous pneumonia and foci of

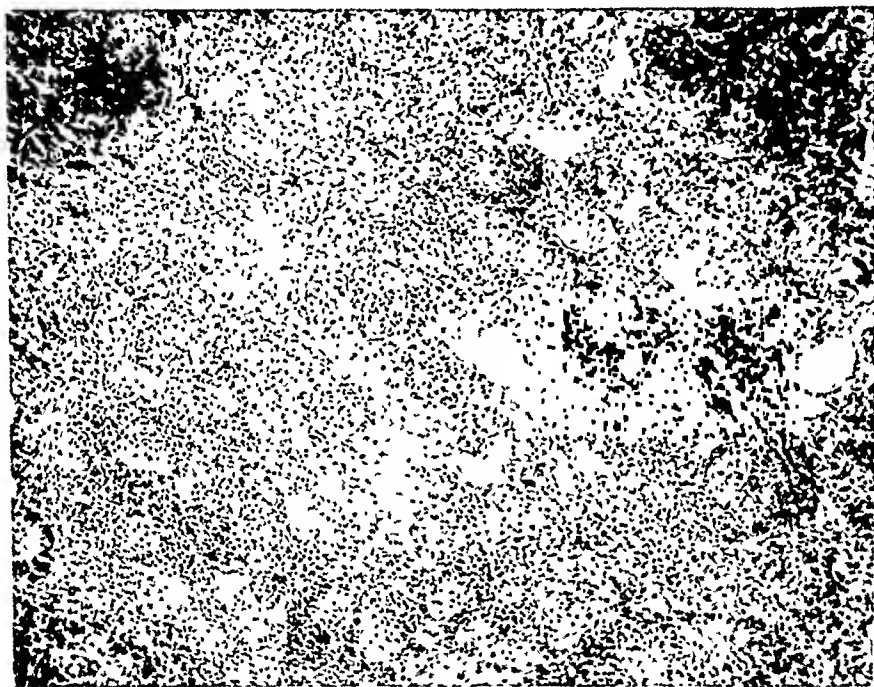


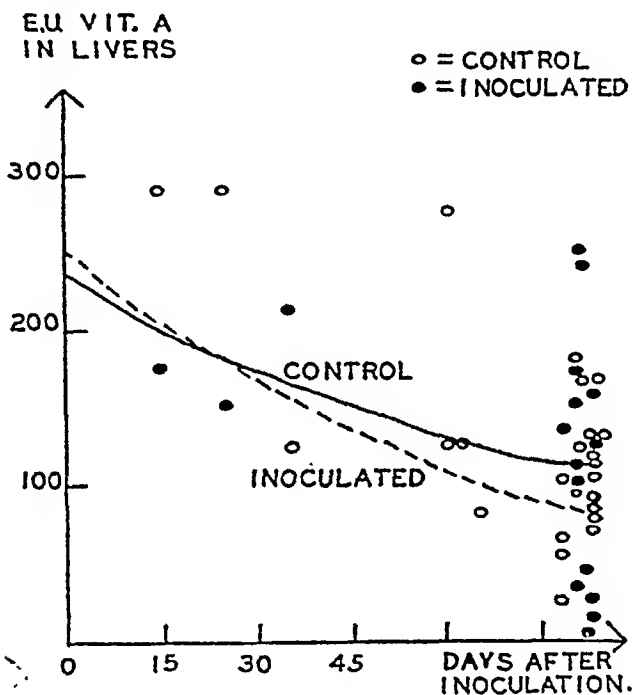
FIG. 2. Section of lung from an inoculated rat which shows the cellular exudative process.

nuclear fragmentation such as are seen in human tuberculosis, especially of sinus tracts. Nodular areas and giant cells are present. If the rats had been allowed to survive longer, it is possible that lesions more closely resembling those of human tuberculosis would have been produced. However, even if the rats have adequate reserves of vitamin A, Steenbock's vitamin A-free diet does not prove suitable when ingested for too prolonged periods. From the autopsies, it was concluded that the involvement had remained localized in the lungs for the most part.

The rate of decrease of vitamin A in the livers of the rats during the eighty-three days of the experiment is shown in graph 4. The open circles represent the values for the control, and the black circles, the values for the inoculated rats.

The mean of the time the control rats lived was seventy days, and the mean of the amount of vitamin A in their livers was 143 E. U., while the corresponding values for the inoculated animals were seventy-three days and 126 E. U.

To obtain the curves shown in graph 4, it is assumed that the rate of decrease of vitamin A in the tissues depends upon the amount present. Then  $V = V_0 e^{-Kt}$ , where  $V$  = the amount of vitamin A in the liver, and for the control group,  $V_0 = 237$  E. U., the average initial amount of vitamin A in the livers,  $K = 0.00955$ , and  $t$  = time in days.  $V_0$  and  $K$  are calculated from the data by the method of least squares, to give the best fit to the equation  $\log V = \log V_0 - Kt$ . For the livers of the inoculated group,  $V_0 = 252$  E. U., and  $K = 0.01296$ . The



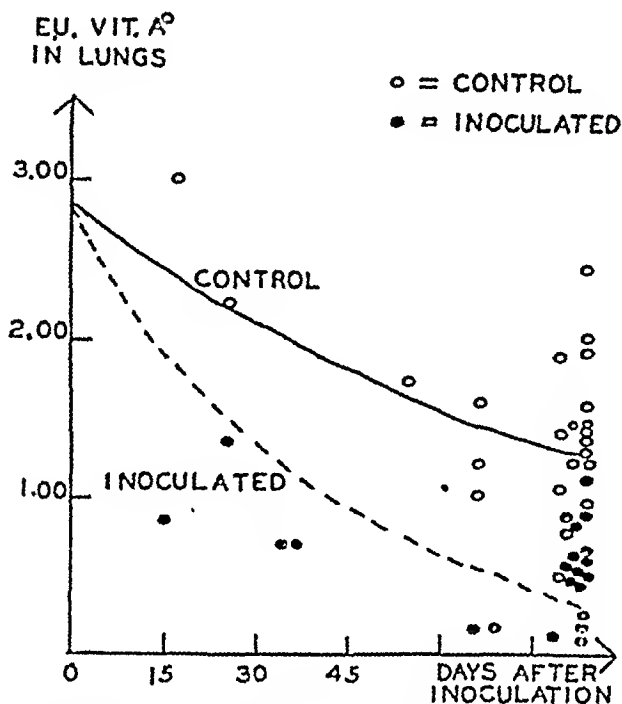
GRAPH 4. The rate of decrease of vitamin A in the livers of rats after intranasal inoculation with tubercle bacilli.

curves show that the amount of vitamin A in the livers of the inoculated animals decreased more rapidly than in the livers of the controls.

Graph 5 shows similar curves for the lungs of the rats. For the control group,  $V_0 = 2.87$  E. U. and  $K = 0.00977$ , and for the inoculated group,  $V_0 = 2.87$  E. U., and  $K = 0.0248$ . The vitamin A in the lungs of the inoculated rats also decreased more rapidly than that in the lungs of the controls. The mean content of vitamin A in the lungs of the normal rats was 1.60, and in those of the inoculated rats, 0.56 E. U.

In the control rats, the coefficients of correlation between the amount of vitamin A in the livers and lungs, and the number of days the rats lived were, respectively,  $-0.754$  and  $-0.595$ . In the inoculated rats, these coefficients were,

respectively,  $-0.279$  and  $-0.336$ . The less satisfactory coefficients of correlation in the case of the latter rats are due in part to the fact that the animals which suffered less severely lived for longer periods.



GRAPH 5. The rate of decrease of vitamin A in the lungs of rats after intranasal inoculation with tubercle bacilli.

#### COMMENTS

The rapidly fatal course of the reaction in the mice was somewhat similar to the results reported by Glover (4). He allowed mice to inhale an aerosol mist of tubercle bacilli and found that the mice began to die eighteen days later and that all died within sixty days. The lesions in the lungs of our rats corresponded to those found by various investigators.

From a consideration of graphs 1, 2 and 3 it is concluded that vitamin A in the livers and lungs of the mice was destroyed as a result of the inoculation, and that the mice which received the high vitamin A diet were more resistant to the effects of the inoculation. Graphs 4 and 5 give evidence that a similar loss of vitamin A occurred in the livers and lungs of the experimental rats. Analysis of the bodies of the mice and rats showed that the vitamin A had not been mobilized from the livers and lungs to other parts of the body, but had actually been destroyed as a result of the inoculation.

It therefore seems justifiable to assume that patients suffering from tuberculosis metabolize more vitamin A than do normal persons. Since these patients, particularly those with tuberculosis of the intestinal tract, do not absorb vitamin A

well when it is given by mouth, it is suggested that they be given relatively large doses of the vitamin by mouth, and that, in some cases, it may be wise to administer the vitamin parenterally.

#### SUMMARY

Mice and rats were inoculated intranasally with virulent human tubercle bacilli. Many of the animals died. The involvement remained mostly localized in the lungs. The lesions in the lungs indicated a reaction to viable, if not actually multiplying, tubercle bacilli. The stores of vitamin A in the animals were depleted as a result of the inoculation.

#### SUMARIO

Ratones y ratas fueron inoculados intranasalmente con bacilos tuberculosos humanos virulentos, muriendo muchos de los animales. La invasión permaneció localizada mayormente en los pulmones, cuyas lesiones indicaron reacción a bacilos tuberculosos, viables si no en realidad en vías de multiplicación. A consecuencia de la inoculación casi se agotaron las reservas de vitamina A de los animales.

We wish to express our great thanks to Dr. Sidney C. Madden, who interpreted the microscopic sections; to Dr. Carl Nielsen of the Abbott Laboratories, who provided us with the fish liver oil used in the experiments; to Mrs. Alice D. Leahy and Miss Elizabeth Day for assistance in carrying out the work.

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## DR. WILLIAM CHARLES WHITE

### Resolution Covering His Resignation as Chairman of the Medical Research Committee of the National Tuberculosis Association

March 1, 1946

On March 1, 1946, Dr. William Charles White's resignation as Chairman of the National Tuberculosis Association's Committee on Medical Research was formally accepted. In recognition of Doctor White's service and accomplishments, the Committee adopted the following resolution which, on March 8 and 9, 1946, was formally endorsed by the Board of Directors of the Association at its meeting in the Hotel Stevens, Chicago, Illinois:

WHEREAS, Dr. Wm. Charles White, retiring Chairman of the Committee of Medical Research of the National Tuberculosis Association, has completed more than a quarter of a century of distinguished service in that position, and

WHEREAS, During that period his unswerving devotion to scientific research and the campaign against tuberculosis has led to notable advance in both fundamental science and the control of that disease, and

WHEREAS, This unswerving loyalty to the National Tuberculosis Association has led to steady advancement in the program of that Association, and

WHEREAS, He has developed an impressive research organization, comprehensive in scope, and by aligning investigators in the basic sciences with experts in technical tuberculosis research has introduced new methods and team-work in medical investigation, and

WHEREAS, His personal and professional association with the United States Public Health Service, National Research Council and other distinguished bodies has been of inestimable value to the National Tuberculosis Association in coordination of effort against tuberculosis, and

WHEREAS, His understanding of the long-range interests of science and technical achievement in the control of tuberculosis led him to a unique and fruitful interest in the development of young men and women who have since become leaders in their respective fields, therefore

BE IT RESOLVED, That the National Tuberculosis Association express to Dr. White and his faithful secretary and daughter, Mrs. Hugh T. Nicolson, its deep appreciation of the service they have rendered to the Association and its confidence that the organization he has developed and results obtained will be of permanent value in scientific research and the control of tuberculosis.

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Dr. H. Stuart Willis, Superintendent and Medical Director of the Wm. H. Maybury Sanatorium, Northville, Michigan, was appointed *Ad Interim Chairman* of the Committee by Mr. Will Ross, President of the National Tuberculosis Association.

## AMERICAN TRUDEAU SOCIETY

### Report of the Missouri-Indiana-Illinois Therapy Conference

#### *Conference Committee*

Dr. Herbert L. Mantz

Dr. George D. Kettelkamp

A tristate conference on tuberculosis therapy was held at the Coronado Hotel, St. Louis, Missouri, on Saturday and Sunday, February 9 and 10, 1946. Missouri was represented by 23 delegates, Indiana by 14 and Illinois by 12. In addition, 9 guests were present from other states, several of whom acted as moderators during the various sessions.

Conferences were held on Saturday morning, afternoon and evening, and on Sunday morning and afternoon. Luncheons on the two days also were attended by all the delegates.

At the close of the Sunday morning session, a short business meeting was held with Dr. Herbert L. Mantz presiding. At this time, it was unanimously voted that such regional conferences are very beneficial and instructive. It was also voted that a similar meeting should be held next year. It was recommended (1) that each of the presidents of the three State Trudeau Societies appoint a committeeman from the members of their society; (2) that these three men, from the respective Trudeau Societies, coöperate in arranging the time, place and choice of delegates for the next meeting; and (3) that the chairmen of the state committees, acting for this present meeting, present these recommendations for action to their respective Trudeau Societies.

The material for this conference consisted of the roentgenograms and records of 75 consecutive admissions, beginning January 1, 1944, from one sanatorium from each of the three states represented. Each sanatorium was allotted approximately four hours for the presentation. Mimeographed sheets containing the pertinent clinical and laboratory findings of each case, in outline form, were distributed to each delegate. At each of the sessions one of the guests was designated to act as chairman or moderator.

Discussion of the cases took place at the time of the presentation. Whenever there was too wide-spread disagreement among the delegates, a vote on the point at issue was called for by the chairman. Occasionally a vote by states was called for. It was of interest that no great discrepancies were noted among the states. Disagreements, when they did occur, did not seem to follow any geographical pattern. They were between individual workers.

Dr. Samuel S. Romendick presented the cases from Robert Koch Hospital, St. Louis, Missouri, during the Saturday morning and early part of the afternoon meetings. Dr. John D. Steele, Milwaukee, Wisconsin, acted as moderator during the Saturday morning session, and Dr. John W. Towey, Powers, Michigan, during the afternoon period.

Dr. H. B. Pirkle presented the cases from the Indiana State Sanatorium, Rockville, Indiana, during the remainder of the Saturday afternoon and evening sessions. Dr. Helen A. Dickie, from Madison, Wisconsin, was moderator during the evening meeting.



Dr. Charles K. Petter presented the cases from the Lake County Tuberculosis Sanatorium, Waukegan, Illinois, during the Sunday morning session. Dr. G. A. Hedberg, Nopeming, Wisconsin, was moderator of this meeting.

Sunday afternoon was reserved for a general summation of the pertinent, debatable points raised by the various cases presented. At this time free discussion again took place with most of the delegates taking part. However, the various extraregional guests led the discussions.

Following this, an informal talk was given by Dr. John B. Barnwell, Director of the Division of Tuberculosis of the Veterans' Administration, on the plan and policies of the new tuberculosis program for the Veterans' Administration. Briefly, there are to be regional Tuberculosis Consultants appointed for each thirteen districts. There will also be more liberal interchange of conferences between Veterans' Hospitals and civilian hospitals, medical schools and clinics. Every Veterans' Hospital will be equipped with a 4 x 5 inch photofluorographic unit. Every admission to Veterans' Hospitals or outpatient clinics will be X-rayed. All patients at Veterans' Chronic Hospitals will be X-rayed at least once each year. An appeal was made for qualified physicians to join the Veterans' Administration.

In general, some of the significant considerations brought out by this conference as noted by this observer were as follows:

(1) Many sanatoria require repeated negative sputum and gastric cultures before pronouncing a patient as an "arrested case." Concentrated sputum examinations alone are deemed inadequate.

(2) All three sanatoria represented had a large percentage of their cases leaving the institution against advice. This situation was deplored and various remedies were suggested. Chief among these is better state-wide control of open cases of tuberculosis. It was the consensus that some form of state-wide disciplinary or even penal action be taken against open cases who refuse to come to a sanatorium or who leave the institution against advice.

(3) The majority of all cases presented were far advanced and most of them were in a desperate condition on admission to the sanatorium. This further emphasized the necessity for early diagnosis and the need for the Public Health Administrators to force patients to subject themselves for treatment promptly after diagnosis.

(4) The general trend among most of the discussants, especially the guests from the other states, was that they are using pneumothorax much less frequently than in the past. Consequent with this decline in the number of pneumothoraces, there was a corresponding decline in the incidence of empyema. It was further emphasized that unless a pneumothorax is good anatomically and gives a good collapse of the diseased areas or will, when improved by early pneumonolysis, it should be abandoned promptly in favor of other forms of collapse therapy, principally thoracoplasty.

(5) Primary thoracoplasty, in cases with unilateral, large (over 4 cm.) and thick-walled cavities, was recommended. It was felt that pneumothorax in such cases was usually unsatisfactory and that a thoracoplasty offers the patient a much better chance for recovery.

(6) Thoracoplasties, when done, should, in most instances, be radical with removal of the transverse processes and the costal cartilages. Incomplete thoracoplasties are usually unsuccessful in controlling the disease. Subsequent operations (revisions) are usually needed to control the disease in such instances.

(7) The opinions on the advisability of phrenic nerve operations, in minimal cases, was about equally divided. Many believed that phrenic nerve interruptions prior to thoracoplasty lead to more atelectasis with retention of secretions in the involved lung and, hence, should not be done.

(8) An initial period of absolute bed-rest was deemed advisable for all patients, unless contraindicated by certain special considerations.

(9) Extrapleural pneumothorax and excisional surgery (pneumonectomy and lobectomy) have a place in tuberculosis therapy, but only in certain selected cases, as a more or less desperate measure.

(10) Bronchoscopies are being done with greater frequency. At some institutions bronchoscopy is done routinely before any collapse therapy. Most delegates were of the opinion that, in the presence of endobronchial tuberculous disease, pneumothorax is contraindicated.

#### *Acknowledgment*

An eight-panel viewing box used at the conference was furnished through the courtesy of the General Electric X-ray Corporation.

SAMUEL S. ROMENDICK, M.D.  
Koch, Missouri

## NOTICE

### United States Public Health Service

Announcement is made by Surgeon General Thomas Parran of the U. S. Public Health Service that a grant for the establishment of 125 Fellowships to train physicians and sanitary engineers in public health has just been approved by the National Foundation for Infantile Paralysis.

Each Fellowship provides a year's graduate training in a school of public health or a school of sanitary engineering. The Fellowships will be administered by the Committee on Training of Public Health Personnel, which consists of representatives of schools of public health, the State and Territorial Health Officers, the American Public Health Association and the U. S. Public Health Service.

The Fellowships are available either during the academic year beginning in the fall of 1946 or the fall of 1947, and are open to men and women, citizens of the United States under 45 years of age.

The purpose of the Fellowships is to aid in the recruitment of trained health officers, directors of special medical services, and public health engineers to help fill some of the 900 vacancies in public health medical positions and 300 vacancies for public health engineers, existing in State and local health departments over the country. The Fellowships are reserved for newcomers to the public health field, and are not open to employees in State and local health departments, for whom Federal Grants-in-Aid are already available to the States.

Applicants for Fellowships may secure further details by writing to the Surgeon General, U. S. Public Health Service, Attention: Public Health Training, 19th and Constitution Avenue N.W., Washington 25, D. C. Owing to the anticipated heavy enrollment in graduate schools, completed applications for training in the fall term of 1946 should be filed promptly. The awards committee will act on applications on the following dates: June 15, July 1, July 15 and August 1.

# THE AMERICAN REVIEW OF TUBERCULOSIS

## ABSTRACTS

VOLUME LIV

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ABST. No. 1

**Treatment of Tuberculous Cavities.**—The biological and physical factors in the genesis of cavities are discussed. The therapeutic approach differs in that the patient with cavities of biological pathogenesis (caseous destruction) should receive total treatment for tuberculosis—both as a generalized disease and as a local affection. In the cavity of physical or mechanical genesis (distensible, nonretractile) the local aspect is the principal one to be solved, and earns the designation of a separate disease. The best approach to the handling of the cavity is to set down a basic treatment for all cavity lesions and determine later with precision the subsidiary or substitutive procedures applicable within the anatomical-clinical indications. Cavities are classified essentially into soft or hard walled ones as recognized radiographically. Also considered are manifestations of insufflation of the cavity, patency of draining bronchi and intracavitary tension. Treatment is classified into 5 groups: direct pneumolytic intervention (open, closed, subfascial, extrafascial, and intramural pneumolysis), functional intervention (phrenic and other nerve- and muscle-operations), plastic operations, direct treatment of the cavity (open drainage, sclerosing, antiseptic, or filling substances, Monaldi type drainage, intracavitary cauterization, ligature of draining bronchus, internal plugging of the draining bronchus), and excisional surgery. The routine study of the patient recommended includes gas analysis and manometry of intracavitary gas, cavernoscopy to study the internal surface of the cavity and the opening of the draining bronchus, the coexistence of bronchial tuberculosis, and the mental, socio-economic

and environmental factors. The basic routine for all cavity cases is three-fold: hygienic-dietetic (rest, position, diet), pneumothorax and whatever medicinal or climatic therapy may be applicable. Other procedures are considered subsidiary or as substitutes and are considered when intrapleural pneumothorax has failed. Some of them are as follows: Operable adhesions should be attacked in the second or third month of pneumothorax. Thoracoscopy should be done in cases of uncollapsed lower lobe cavities even though no adhesions are seen, as they are often invisible radiographically. For the inoperable types of apico-costal adhesions, extrapleural pneumolysis is recommended. The handling of other inoperable adhesions depends on the type and location of the cavity. An extrapleural pneumothorax is recommended in the apical soft walled cavity. If the lesions extend to the base of the upper lobe or lower, a mixed pneumothorax is done, extrapleural above and intrapleural below with either independent pockets or preferably communicating ones. The hard walled upper lobe cavity is handled by a partial thoracoplasty. For the bilateral case combinations of intra- and extrapleural pneumothorax, sometimes with phrenic nerve operations are considered. In general when the extent of disease in a bilateral case contraindicates bilateral pneumothorax, it also contraindicates use of any of the subsidiary or substitutive measures. Bilateral thoracoplasty is not favored. Considerable space is given to a consideration of cases where pneumothorax is ineffective despite the absence of adhesions. Such cases are due to elastic atony or retractile inertia of the lesion, or to bronchial obstruc-

tion. Bronchoscopy with treatment of bronchial lesions is indicated unless the cavity is peripheral when thoracoplasty should be done. Otherwise pneumothorax may be continued. When pneumothorax is impossible because of pleural symphysis, extrapleural pneumothorax should be done for recent upper lobe cavities and thoracoplasty for old ones, phrenic nerve interruption for lower lobe cavities. For ipsilateral resistant bronchial lesions in this group, thoracoplasty is recommended. When an extrapleural pneumothorax is not effective because of extent of disease, phrenic interruption might help as an adjunct although the choice would be to abandon the pneumothorax and do a thoracoplasty. Subsidiary and substitutive procedures to phrenic paralysis are listed as: bed-rest (lateral position), pneumoperitoneum, extrapleural pneumothorax, thoracoplasty, transparietal aspiration or lobectomy. In thoracoplasty failures, the following are recommended: revision with or without ligature of lung stump, phrenic interruption, transparietal aspiration, open drainage, lobectomy or pneumonectomy. Excisional surgery is termed radical. Prompt and adequate treatment is stressed in any type of lesion.—*Sistematica del tratamiento de la caverna tuberculosa del pulmon, R. F. Vaccarezza & O. A. Vaccarezza, Prensa med. argent., May, 1945, 32: 785.—(J. S. Peterson)*

**Treatment of Tension Cavity.**—Institution of a pneumothorax in a patient with cavity pulmonary tuberculosis and subsequent pneumonolysis caused the cavity to increase in size and to assume the characteristics of a tension cavity. Five-tenths mg. of atropine sulfate was injected intravenously daily and small refills were given more frequently. After two weeks of such treatment the cavity disappeared. It is assumed that the beneficial effect in this case was due to the relaxation of the bronchial tree and the subsequently improved bronchial drainage of the ballooned cavity.—*Actions des injections endoveineuses d'atropine et des insufflations pleurales rapprochées sur une caverne ballonnée, M. Baričty, R.*

*Lezobre & P. Choubrac, Rev. de la tuberc., 1928, No. 4/6, 8: 76.—(G. Simmons)*

**Horner's Syndrome following Pneumonolysis.**—Horner's syndrome appearing after successful intrapleural pneumonolysis was observed in 4 cases. Nervous fibres from the cilio-spinal centre pass into the anterior branches of the first three dorsal nerves, reach the stellate ganglion and finally the cervical sympathetic structures. Vieregg's nerve unites the middle and the inferior cervical ganglions or the inferior cervical and the first thoracic ganglions. Fibres innervating the iris pass through this nerve. During a high intrapleural pneumonolysis the stellate ganglion, Vieregg's nerve or communicating branches may be injured. When the stellate ganglion is injured, there may be vasomotor disturbances in the corresponding upper extremity. In all cases symptoms (ptosis, myosis and vasodilatation on the involved half of the face) subsided within a few weeks.—*Le syndrome de Claude Bernard-Horner consécutif à l'opération de Jacobatus, Ch. Hanrich, Y. Bourrain & G. Roche, Rev. de la tuberc., 1948, No. 4/6, 8: 55.—(G. Simmons)*

**Mobility of Cavities during Cough.**—Two hundred and eighty-two patients were studied regarding cavity mobility during cough on fluoroscopy. (Sign of Brissaud). In the assumption that the mobility of a lesion during cough depends on the presence of a free pleural space, the value of the sign was verified in patients before and after attempt of pneumothorax. If there is complete mobility, the movements of a cavity during cough are opposite to the movements of the ribs in all positions of the patient behind the fluoroscopic screen. Cavities were classified in three categories: (1) cavities remaining immobile during cough in all fluoroscopic positions, (2) cavities with partial mobility showing the sign of Brissaud in one or the other position, (3) mobile cavities, showing motion in all positions. In 151 cases with immobile cavities subsequent pneumothorax was ineffective in 95 per cent of cases. In 56 cases with partially mobile cavi-

tics pneumothorax was ineffective or impossible in 50 per cent, effective in 50 per cent. In 75 cases with mobile cavities pneumothorax was effective in 90 per cent, ineffective or impossible in 10 per cent. It seems therefore that in the presence of total or absent mobility rather definite conclusions can be drawn as to the possibility of pneumothorax, whereas partial mobility gives no sure indications. The value of pneumothorax in these cases will depend on the feasibility of a pneumonolysis. Comparison of cavitory mobility before and after pneumothorax reveals that a small number of previously immobile cavities became partially or completely mobile after institution of pneumothorax. Using cavitory mobility as an indication for the possibility of a pneumonolysis the following correlations were found: in 78 cases of immobile cavities pneumonolysis was impossible in 89 per cent. An effective partial pneumonolysis could be performed only in 7 per cent. In 55 cases with mobile cavities pneumonolysis was not necessary in 51 per cent. Complete pneumonolysis could be performed in 16 per cent, partial pneumonolysis in 27 per cent. In this group, 83 per cent of pneumothoraces were effective. The sign of Brissaud, indicating the condition of the pleural space, can be of practical help in various situations. A freely moving cavity may suggest to reattempt pneumothorax in spite of several previous failures. In case of a giant cavity with good mobility the risk of pneumothorax will be more easily accepted, whereas with doubtful or absent mobility thoracoplasty will be preferred. If cavitory lesions develop on the contralateral side of a pneumothorax, cavitory mobility will help to decide on a delay before institution of the second pneumothorax. This delay should not be prolonged, if one observes diminution of cavitory mobility, indicating formation of adhesions. In cases with bilateral involvement for which bilateral pneumothorax is considered, it is advised to attempt pneumothorax on the side where more adhesions can be expected according to the sign of Brissaud. If pneumonolysis is impossible on this side, it will be useless to induce the second pneumothorax. Cavitory mobility

after institution of pneumothorax gives indications about presence, form and type of adhesions as well as the possibility and usefulness of pneumonolysis.—*Quels renseignements peut-on tirer avant et après la création du pneumothorax artificiel de la mobilité cavitaire a la toux?* P. Langeard, *Rev. de la tuberc.*, July-October, 1941, 6: 485.—(V. Leites)

**Paralysis of Diaphragm during Pneumothorax.**—The concept of the diaphragm as an organ of respiration is inadequate. Lemon demonstrated the fact that intercostal action could adequately compensate for bilateral diaphragmatic paralysis in dogs. In humans only a slight temporary lowering of the vital capacity is noted after unilateral phrenic paralysis. Lemon believes that an important diaphragmatic function is to aid in the maintenance of the intraperitoneal pressure and to transmit this pressure to the abdominal organs wherever and whenever necessary. Digestive disturbances follow not only left phrenic paralysis, but also left pneumothorax. The author noted a measurable decrease in bilateral diaphragmatic excursions following each pneumothorax refill. The decrease was more notable on the collapsed than on the uncollapsed side. Therefore, the mobility of the diaphragm depends not only on its own contractile power and an intact phrenic nerve, but also on the level of intrathoracic pressure. Patients with left pneumothorax may have anorexia or a sense of fulness after having eaten but a small amount. The supposition is that a depressed, immobile diaphragm serves to limit the adaptability of the stomach to increasing contents. Three case histories are presented which emphasize the syndrome of anorexia accompanied by loss of weight and strength unrelated to active disease, but occasionally observed in left pneumothorax. Mechanical paralysis of the diaphragm may be especially important during the period of rehabilitation when nutritional demands are increased.—*Mechanical Paralysis of the Left Hemidiaphragm Complicating Collapse Therapy in Pulmonary Tuberculosis*, O. Feinsilver, *Dis. of*

*Chest*, March-April, 1945, 11: 188.—(K. R. Boucot)

**Air Embolism in Pneumothorax.**—Six instances of air embolism occurring among 950 patients receiving pneumothorax in the Municipal Institute of Tuberculosis in Buenos Aires are reported. One accident occurred during the initial pneumothorax treatment, one during the third, and the others later. The severity of symptoms varied. One patient died with a spastic monoplegia fifteen days after the accident with symptoms of a bronchogenic spread. Another patient died within two months, embolic signs having lasted four days. At the moment of the accident all patients had similar symptoms: pallor, sweating, rapid, thready pulse, loss of consciousness, etc. Twenty-four hours later symptoms were most varied. Neurological signs were contralateral to the side of the pleural puncture. Two patients had monoplegias lasting about two weeks. In all patients, there was an interval of two to five minutes between the moment of pleural puncture and the appearance of the first symptom. Evidently the nervous reflexes arise not from the pleura but from the central nervous system. The accident frequently occurs in patients whose pulmonary lesions are complicated by numerous adhesions which prevent an adequate collapse. After reviewing the experimental work of the Frenchmen, Villaret and Cachera (1937, 1938), and the Brazilians, Amorin and Branco, on air embolism in dogs and rabbits, the authors conclude that air emboli and not pleural shock account for the great majority of accidents during therapeutic pneumothorax. They state that air must be introduced into a pulmonary vein to produce the cerebral emboli which cause focal organic lesions and a series of symptoms. By way of prophylaxis, difficult or ineffective pneumothoraces should be abandoned. When an accident occurs, cardiac stimulants such as camphor or ergotamin tartrate are advised. Adrenalin should never be used.—*Nuestra experiencia sobre los accidentes nerviosos del neumotorax artificial*, I. M. Hernandez & I. Smirn-

*off, Arch. argent. de fisiol.*, October-December, 1944, 20: 419.—(R. Kegel)

**Extrapleural Pneumothorax.**—Reviewing end-results in 115 patients in whom an extrapleural pneumothorax had been established, the following conclusions are arrived at: (1) In 5 cases of early tuberculosis the results obtained were good. (2) Among the 35 cases of old stabilized lesions, good results were obtained in 24 (69 per cent); there were 4 deaths and in 7 the results were unsatisfactory. (3) In 68 cases no other collapse therapy could have been instituted. In 36 cases of this group (53 per cent) the results obtained were good.—*Résultats de 115 cas de pneumothorax extra-pleural*, A. Maurer & J. Chenebault, *Rev. de la tuberc.*, 1941, No. 5/6, 6: 370.—(G. Simmons)

**Extrapleural Pneumothorax.**—Thirteen cases of extrapleural pneumothorax, established during the period 1937-1939, are analyzed. In 5 cases the lesions were recent but progressive, in 2 recent and stabilized and in 6 the lesions were cavity and old. In 3 cases large cavities were present. Complications encountered were: (1) Extrapleural hemorrhages and infection: 2 cases. (2) Secondary infection of the extrapleural space: 3 cases. Four patients thus treated have been considered cured for three years. In one patient the pneumothorax is being abandoned. In 4 others it is being maintained with good results and in 4 an oleothorax has been substituted. In all cases the results obtained are called "perfect." Reexpansion of an extrapleural pneumothorax always occurs from below upward and from the front toward the back. Extrapleural effusions become localized in the superposterior portion of the chest and cause considerable thickening of the pleura, which interferes with the reexpansion of the lung and may result in retraction of the ribs and of the mediastinum. In uncomplicated cases and in those in which no conversion into an oleothorax had become necessary, thickening of the pleura and thoracic retraction are insignificant. Contralateral spread was observed in

only one case. The advantage of extrapleural pneumothorax over thoracoplasty is stressed with the assumption that after reëxpansion of the lung there is "complete functional recovery of the lung, identical to that obtained with an intrapleural pneumothorax."—*Resultats éloignes du pneumothorax extra-pleural. (13 observations de malades opérés depuis plus de quatre ans.)*, Ch. Gernez-Rieux, P. Razemon & R. Garcenot, *Rev. de la tuberc.*, 1943, No. 7/9, 8: 127.—(G. Simmons)

**Histology of Extrapleural Pneumothorax.**—The original extrapleural cavity is a wound space. Its walls undergo gradual histological changes to adapt the space to the function which it is to perform. Biopsy specimens taken at operations months and years after the original operation show that macroscopically the wall is smooth and glistening and indistinguishable from true pleura. Microscopically layers of collagenous and elastic fibres are discernible, and in 10 out of 15 cases a mesothelial covering was present. This consisted of flat or cuboidal cells, from one to several layers deep. These cells look like epithelial cells. It is likely that these layers originate from undifferentiated cells of mesenchymal origin which are found in connective tissue. In some cases the mesothelial lining was absent and the surface was formed by layers of connective tissue fibres.—*Histologische Untersuchungen der Wand des extrapleuralen Pneumothorax*, R. Fink, *Schweiz. med. Wchnschr.*, September 30, 1944, 74: 1029.—(H. Marcus)

**Spontaneous Extrapleural Pneumothorax.**—The case of a 28 year old female is reported who subsequent to an intrapleural pneumolysis developed an empyema which was treated with repeated aspirations. She developed a tumor-like formation of the breast which proved to be a small extrapleural pocket containing air under positive pressure (+35) much higher than the intrapleural pressure (+5). Subsequently a cold abscess developed from this extrapleural pocket and became localized within the parenchyma of the right

mammary gland.—*Un cas d'empyème tuberculeux d'origine pleurale ayant provoqué la formation d'une poche aérienne extrapleurale puis celle d'une collection purulente intramammaire secondairement fistulisée*, A. Clermont, *Rev. de la tuberc.*, 1941, No. 5/6, 6: 364.—(G. Simmons)

**Brain Abscesses following Monaldi Drainage.**—This complication of Monaldi drainage has not been reported heretofore, but it has been observed twice by the author. In the cases under consideration, the cavities had decreased markedly in size following suction drainage, but the bronchi remained open. In one case the catheter was removed and an attempt was made to replace it. This was followed by slight bleeding. In the other case the catheter became blocked and it was attempted to reëstablish drainage by flushing it. This was also followed by slight bleeding. Within a short time of this occurrence symptoms of brain abscess were noted, and death occurred within due time. On theoretical grounds alone, abscess should occur from time to time, just as it does in bronchiectasis. Trauma and bleeding must be avoided in manipulation of the catheter, as the capillary network around the cavity is extremely rich and is practically in communication with the cavity.—*Hirnabszesse als Komplikation bei der Kavernensaugdrainage nach Monaldi*, F. Strmen, *Schweiz. med. Wchnschr.*, November 18, 1944, 74: 1197.—(H. Marcus)

**Air Embolism following Cavity Aspiration.**—On theoretical grounds one might expect air embolism quite frequently as a complication of cavity aspiration in preparation for Monaldi drainage. Actually it is quite rare so that its occasional occurrence has not acted as a deterrent from a therapeutically sound procedure. To further minimize the chances for its occurrence, it is advisable to operate on a patient who is lying down. The patient has to be prevented from getting up at any time during the procedure and for one-half hour following it. Sufficient opiate should be given to prevent cough. A case is reported where the pa-



tient died shortly after the exploratory needle had been placed into the cavity. Autopsy showed that the needle had penetrated a small pulmonary vein. Bleeding into the cavity had occurred, and this had stimulated cough. The high pressure during cough had forced air from the cavity into the open blood vessel. The brain showed that the blood vessels of the pia-arachnoid and the base of the brain were filled with air bubbles.—*Über eine tödlich verlaufende Luftembolie nach Kavernenpunktion*, H. Mauderli, *Schweiz. med. Wchnschr.*, November 18, 1944, 74: 1190.—(H. Marcus)

**Cavernostomy.**—A big tuberculous cavity was opened with a galvanocautery. The walls and the bronchial openings were cauterized and the cauterizations were repeated eight times. Five months later there was no evidence of a pulmonary cavity except for a scar. It is believed that the indications for cavernostomy and cauterization of the cavity walls should be enlarged.—*La spéléotomie large dans le traitement des cavernes tuberculeuses du poumon*, A. Bernou & R. Goyer, *Rev. de la tuberc.*, 1943, No. 4/6, 8: 71.—(G. Simmons)

**Cavernostomy.**—In 4 cases of large residual cavities persisting after thoracoplasty cavernostomy was performed. The cavity was opened widely. The walls and the draining bronchi were cauterized. In all 4 cases complete and persistent closure of the cavities was obtained. The necessity for a wide opening of the cavity and for a thorough cauterization is emphasized.—*Quelques exemples de spéléotomie pour cavernes résiduelles sous thoracoplastie*, A. Bernou, R. Goyer & L. Marceaux, *Rev. de la tuberc.*, 1944, No. 1/3, 9: 24.—(G. Simmons)

**Pulmonary Resection for Tuberculosis.**—With the improvement of operative and anesthesia technique, resection in pulmonary tuberculosis has become a reasonable procedure. Although the immediate mortality has been greatly reduced, the late results are at present unknown. From scattered case reports it would appear that the patient may be in danger of fistula formation, reactivation and

spread for years after the operation. There is still considerable controversy as to whether elective resection is a sound procedure. The majority of workers in the field feel that lobectomy should not be done if a cure by thoracoplasty appears likely. The procedure should be reserved for lower lobe cavities, located either near the mediastinum or in the middle portion of the lung. It would appear to be the ideal treatment for tuberculoma, but this condition is rarely diagnosed preoperatively. Its value in cases of bronchial disease is still disputed since persistent bronchial tuberculosis of the stump, with reactivation, is occasionally seen. The author reports on 9 cases, with one fatality. Three of the 8 surviving cases developed bronchial tuberculosis, but the overall result was satisfactory in all 8 patients. Only one upper lobe removal is among this series, and in this case thoracoplasty was refused by the patient and lobectomy was elected. The other 8 cases represent lower, or lower and middle lobe removals.—*Resection of the Lung in the Treatment of Pulmonary Tuberculosis*, O. C. Brantigan, *Arch. Surg.*, October, 1945, 51: 147.—(H. Marcus)

**Pulmonary Resection for Tuberculosis.**—Tuberculous tracheobronchitis is known to present a serious prognosis and a complex therapeutic problem. Collapse procedures not only have limited value in cases of endobronchial tuberculosis, but actually may be dangerous. Because of the high incidence of atelectasis, unexpandable lung, empyema and anaerobic infection, pneumothorax and phrenic paralysis are contraindicated in the face of extensive bronchial ulceration or marked stenosis. Complete thoracoplasty has given by far the best results. However, analyses of reported series suggest that thoracoplasty has been applied to only a fraction of patients with tracheobronchial involvement. Many such cases progress so rapidly as never to be considered suitable candidates for thoracoplasty. The incidence of tension cavities, basal disease and wide-spread active disease is high in patients with bronchial involvement and associated stenosis. They do notably

poorly with thoracoplasty. Thirty pulmonary resections on cases complicated by endobronchial tuberculosis were performed by one of the authors between 1934 and January 1, 1944. Twelve of these were desperate cases operated on as a last resort; 96.6 per cent had positive sputum. The ratio of females to males was 4:1. The majority were in the fourth decade of life. Twenty-four of the 30 had stenotic bronchial lesions of which 11 were associated with ulceration. Five had ulcerative lesions. Only one had a submucosal type of tuberculous bronchitis, and this was associated with a 50 to 60 per cent narrowing of the right upper lobe orifice. Indications for pulmonary resection are: (1) associated suppurative disease; 4 such cases were included in this series; (2) post-thoracoplasty cases with uncontrolled disease; this series included 5; (3) extensive multilobar predominantly unilateral tuberculosis; there were 21 such cases in this series. An analysis of complications is based on whether or not the surgical procedure was done before or after January, 1942. This date was chosen because of the standardization in January, 1942 of operative procedure to the pleural flap method of bronchial closure and individual ligation. In this latter group no wound infection occurred, but one bronchial fistula, 2 empyemata, and 3 instances of postoperative contralateral spread occurred. There were 2 contralateral pleurisies with effusion in the entire series. One of these was positive by guinea pig inoculation. Routine postoperative bronchoscopy revealed ulceration of the bronchial stump in 4 patients, an incidence of 21 per cent. None of these patients had symptoms. Two were positive postoperatively, one by sputum examination, the other by gastric washings. Three of the 4 have been negative following bronchoscopy with application of 30 per cent silver nitrate. Operative mortality for the entire group was 26.6 per cent, or 8 out of 30. All but one of these deaths occurred in the desperate risk cases. Mortality in reasonable risk cases was 5.5 per cent. Three late deaths occurred, all in patients treated prior to January, 1942. This shifts the case mortality to 36.6 per cent. In

the group operated on since January, 1942, one of the 12 reasonable risk cases died of postoperative embolism as contrasted with 4 out of 7 of the desperate risk cases (57.1 per cent). Only 4 deaths in the entire series were attributable to tuberculous infection. Five deaths were related to the surgical problems of pulmonary resection. Eleven out of the whole series of 30 have died. Of the remaining 19, 15 are clinically well, 11 have been discharged from the sanatoria to their homes. The other 4 are still on bed-rest. One has a mixed empyema and is awaiting thoracoplasty, one has ulceration of the bronchial stump, positive sputum, tuberculosis of the ilium and sacroiliac joint, and the other 2 have progressive contralateral lesions. They will eventually die of tuberculosis. Examination of pathological specimens reveals a much higher incidence of tuberculous bronchitis than that diagnosed bronchoscopically. Submucosal involvement with round cell infiltration and usually with tubercle formation is the earliest finding and has frequently been present when unsuspected. Ulceration or granulation merely represented the area where the bronchial disease had become an open focus. This is significant because of the possibility that in bronchial amputation the suture line will go through the involved portion of the bronchus. The draining bronchus of the cavity is involved almost without exception. This is especially notable in lower lobe cavities, most of which are located in the superior division of this lobe. Many of these lesions will not be discovered by bronchoscopy as they are "around the corner." When resection is contemplated in such cases the draining bronchus should be considered to be involved. A middle and lower lobectomy on the right side may be a more rational procedure with this type of lesion than a lower lobectomy because the bronchial suture line can be placed above the involved portion. Parenchymal lesions in the series have been characterized by a high incidence of basal disease with a tendency toward a bronchopneumonic type of tuberculous lesion. Examination of specimens leaves little doubt that, had collapse measures been used in these cases, a

large bulky mass of tuberculous lung would have been collapsed leaving a huge amount of diseased tissue as a threat in the future. Contralateral spread is still a definite threat having occurred in 15 per cent of this entire series and in 15.8 per cent of those with tuberculous bronchitis. At present an attempt is being made to overcome spilling at the time of operation by making bronchial ligation the primary step in resection. The use of intrabronchial anesthesia is anticipated to exteriorize each lung and thus possibly prevent intrabronchial spilling of secretions. Bronchial stump ulcers have occurred in 21 per cent of the series. In each instance endobronchitis had been present prior to resection. Ulcers occurred most frequently where mattress sutures were placed in the bronchus, so now only end sutures are used. The condition of the contralateral lung is of extreme importance though the presence of disease in it does not contraindicate resection. Many cases in this series had contralateral tuberculosis, but only 3 underwent exacerbation. The amount of lung tissue to be resected must be decided upon at the time of operation when the lung can be palpated. Not infrequently considerable unsuspected tuberculosis is found in a lobe necessitating pneumonectomy when only lobectomy had been contemplated. Where endobronchial tuberculosis involves the major bronchi, particularly where stenosis is present, pneumonectomy can be decided upon prior to exploration. On the right side in cases of basal tuberculosis, lobectomy is more feasible than on the left side because the intermediate bronchus is often free of disease. On the left side, lower lobectomy finds a limited field in cases with bronchial lesions and is applicable only rarely where bronchial lesions lie well below the level of the superior division. Case reports are given.—*Pulmonary Resection for Tuberculosis Complicated by Tuberculous Bronchitis (Preliminary Report)*, R. H. Overholt & N. J. Wilson, *Dis. of Chest*, January–February, 1945, 11: 72.—(K. R. Boucot)

**Primary Tuberculous Tracheobronchitis.**—Sixteen cases of primary tuberculous tracheo-

bronchitis were observed. There were no significant antecedents in the history of these patients, except in 2 cases, in which the onset of the endobronchial disease followed three to four years after erythema nodosum. Young females were more often affected than males. The symptoms of the initial ulcero-granulomatous phase were: nonproductive cough of a particularly violent and persistent character, retrosternal burning sensation, paroxysmal dyspnea and discrete hemoptysis. At later stages of the evolution when fibrostenotic changes prevailed, phenomena of bronchial obstruction, wheezing, atelectasis and suppuration in areas distal to the stenosis were observed. On bronchoscopic examination large productive lesions were noted, or in other cases an extensive necrotic caseous bronchitis was found. The sputum was mostly positive on direct examination with abundant acid-fast bacilli. The chest X-ray film showed no changes unless there was marked stenosis. In 6 cases there were no pulmonary lesions on the X-ray film; in 4 cases there was a slight retraction of one hemithorax; in 4 cases atelectasis was present and in 2 cases there was pulmonary suppuration. No tuberculous lung lesions were noted during the period of observation of these cases. The duration of the process of scarring varied from a few months to one and one-half years.—*Tracheobronchitis tuberculosas clinicamente primitivas o puras*, J. C. Dighiero, *Hoja fisiol*, June, 1945, 5: 2.—(L. Molnar)

**Endobronchial Tuberculosis.**—Direct signs of endobronchial tuberculosis are atelectasis, sudden consolidation of a lobe under collapse, sudden spread of an apparently controlled lesion, blocked cavity and far advanced disease. Indirect signs are hemoptysis of mild or streaking type without demonstrable X-ray findings, positive sputum without demonstrable cause or persistent nonproductive cough. Atelectasis may be massive with mediastinal shift or may consist only of small areas often found in apical regions. Blocked cavities and cavities which change in size suddenly may be due to endobronchial tuberculo-

sis either through ball-valve action or by stenosis or kinking of a bronchus. In one institution, 565 patients were bronchoscoped. Of these, 224 were examined routinely prior to thoracoplasty or other collapse procedure. The balance were bronchoscoped because of the above signs and findings. In the 224 cases bronchoscoped prior to collapse, 26 cases of ulceration or stenosis were found. Analyzing this group, of 61 cases with wheeze, 23 had positive bronchoscopic findings of ulceration or stenosis; of 81 with consolidation or atelectasis, 27 had positive findings; of 18 with new disease while the old disease was controlled, 5 had positive findings; of 28 cases without obvious source of hemoptysis, 8 had positive findings; of 50 cases with hilar flare, excessive dyspnea, etc., 17 cases of ulceration or stenosis were found.—*The Radiological Findings in Tracheo-Bronchial Tuberculosis*, C. C. Birkelo & L. A. Poznak, *Dis. of Chest*, January-February, 1945, 11: 26.—(K. R. Boucot)

**Pathology of Tuberculous Tracheobronchitis.**—The material consisted of 110 consecutive cases autopsied at Triborough Hospital for Tuberculosis with death due to tuberculosis. All had pulmonary involvement. Routine microscopic sections were taken from the anterior and posterior walls of the trachea, from the carina, and from both main bronchi as well as from any other grossly suspicious areas. The following lesions were seen: (1) diffuse reddening and edematous thickening of the mucosa (microscopically, these lesions revealed congestion with dense lymphocytic infiltration); (2) microscopic tubercles situated between glands or immediately beneath the epithelium; (3) shallow microscopic ulcerations of the mucosa with lymphocytic infiltration of the ulcer base (unless these revealed the presence of tubercle bacilli, they were not included in this series); (4) shallow microscopic ulcerations with tuberculous granulation tissue in the base; (5) gross ulcerations with tuberculous granulation tissue in the base, the most frequently encountered lesions (occasionally these ulcers had eroded cartilage); (6) ulceration with extensive tuberculous granulation

tissue accompanied by fibrosis leading to some narrowing of the lumen (fibrosis was not marked in the trachea, was more appreciable in the main bronchi, but was only really advanced in degree in the branch bronchi); (7) diffuse fibrotic thickening of the bronchial wall accompanied by some narrowing and by the presence of superficial submucosal tubercles (this was also most marked in the branch bronchi); (8) scarring due to healing (none was seen in the trachea and only occasionally in the main bronchi; only in branches of the lobar bronchi draining tuberculous cavities was complete occlusion seen). The incidence of tuberculous tracheobronchitis was 60 per cent in this series without any noteworthy predisposition according to sex, race or age. There was a preponderance in cases with large pulmonary cavities, 70 per cent, as contrasted with 17 per cent in cases with small cavities. The author believes that primary tuberculous tracheobronchitis is extremely rare. Secondly, it may be due to surface implantation, direct extension, to lymphogenous or hematogenous spread, but surface implantation seems to be the most common mode of infection. She suggests that, in bronchi draining cavities, the tuberculous process diminishes in severity as the main bronchi and trachea are approached. Fifty-seven per cent of the cases had tuberculous laryngitis. Of 54 cases having laryngitis, 13 had no tuberculosis of the trachea or main bronchi, while 18 without laryngeal involvement had tracheobronchial tuberculosis. Therefore, there is no apparent correlation between these two conditions. It is pointed out that autopsy studies have the disadvantage that cases with bronchial disease and minimal tuberculosis are not seen, while clinical investigation is limited to gross inspection and study of biopsy fragments. Therefore, close correlation is necessary between clinical observations and postmortem studies.—*Tuberculosis of the Trachea*, Gertrude Silverman, *Dis. of Chest*, January-February, 1945, 11: 3.—(K. R. Boucot)

**Pathology of Endobronchial Tuberculosis.**—Sixty lungs or lobes of lungs resected for tuber-

eulosis by Dr. Richard H. Overholt and associates were examined. Microscopic study was made of all the main, lobar, and segmental bronchi. Tuberculous endobronchitis was found in 31, or roughly 50 per cent, of the series. Females in the third and fourth decades were particularly affected. All cases with endobronchial tuberculosis had positive sputum. One-third of the patients had had symptoms of tuberculosis for less than one year. All gradations of pathological changes were found between an occasional tubercle and stenosing tuberculous granulation tissue associated with fibrosis. Even with mildly extensive tuberculous involvement there was at times no ulceration or only focal or superficial ulceration. There was apparent continuity of disease from the point of endobronchial tuberculosis nearest the hilum through the segmental bronchi to the parenchymal lesion. Thus, whenever there was tuberculous bronchitis of a main stem bronchus, it was also found in a lobar bronchus. Severity of the disease varied considerably in different parts of the same bronchus. In 20 cases the parenchymal lesion from which the bronchial disease arose was a cavity. In the remainder it was a caseous focus of varying size and age. In 27 of the 31 cases it was possible to examine three or more of the hilar lymph nodes microscopically, and at least one node in each case was tuberculous. There was no instance of direct extension from a lymph node to a bronchus. It was concluded that tuberculosis of the larger bronchi is the result and complication of parenchymal tuberculosis. Observation of the frequency with which tuberculosis involved the hilar nodes proves lymphatic drainage of tubercle bacilli from the pulmonary focus to the hilum. Thus, the entire course of a bronchus, including segmental, lobar, and main stem, which leads from a parenchymal lesion is potentially subject to tuberculosis. The area nearest the pulmonary disease is obviously more subject to infection, accounting for the greater incidence of involvement of segmental bronchi. The bronchus has an ability to heal even when superficial ulceration has taken place. However, when tuberculous granula-

tion tissue has replaced submucosa and mucosa resulting in stenosis, complete healing can only take place by scar tissue formation. Such an area of severe endobronchial tuberculosis may become independent of its apparent parenchymal lesion and act as a focus for further dissemination. Infection of a bronchus by direct implantation might be assumed because all in this series had a positive sputum were it not for the fact that bronchial disease *per se* may give rise to a positive sputum. Such implantation may occur but it was not possible to estimate its incidence from this study. Hematogenous dissemination did not produce bronchial disease in this study.—*Surgical Pathology of Endobronchial Tuberculosis, W. A. Meissner, Dis. of Chest, January-February, 1945, 11: 18.*—(K. R. Boucot)

**Ulcerative Tracheobronchitis.**—Bronchoscopic examinations were done in patients who had had previous episodes of atypical pneumonia followed by delayed convalescence, chronic bronchitis and hemoptyses. Ulcerative lesions of the tracheobronchial tree were found in 9 patients and were believed to be responsible for the protracted course of the disease. Biopsy of the ulcers revealed non-specific granulation tissue and inflammation. These lesions are bronchoscopically indistinguishable from ulcerations due to Boeck's sarcoid, from the chronic infective granulomata or from the blastomycoses. The treatment consisted in bed-rest, high vitamin, high caloric diet, postural drainage, cauterization with silver nitrate and instillation of penicillin. The ulcerations healed within two to four months. Four cases are reported in detail.—*Ulcerative Tracheobronchitis following Atypical Pneumonia: Report of Cases, E. B. Kay, Arch. Int. Med., August, 1945, 76: 93.*—(G. C. Leiner)

**Treatment of Bronchopleural Fistulae.**—Atropine sulfate,  $\frac{1}{4}$  mg. injected subcutaneously, was used repeatedly in the treatment of spontaneous pneumothorax occurring in the course of collapse therapy. In 6 cases there was apparently a favorable response, in 3 cases

no benefit was derived from this treatment. There are no contraindications to the use of atropine sulfate. Dyspnea is always relieved, probably because the bronchi become relaxed, the intrapulmonary ventilation improved and the lung follows the excursions of the thoracic cage better.—*Sulfate d'atropine et perforations pulmonaires*, M. Dussert, *Rev. de la tuberc.*, 1941, No. 5/6, 6: 339.—(G. Simmons)

**Pulmonary Hypoventilation Due to Tuberculous Lymph Nodes.**—In tuberculosis of the tracheobronchial lymph nodes various effects on adjacent bronchi are distinguished. There may be development of a check-valve or stop-valve mechanism, both of which can lead to obstructive atelectasis. The first degree of bronchial obstruction is narrowing of the lumen with conservation of patency during inspiration and expiration. It is believed that this state is not irrelevant for the lung sector supplied by the involved bronchus, but leads to a state of hypoventilation in this area. The following observations were made: the first sign was a definite diminution in the size of a lobe without any noticeable diminution in transparence. Since this phenomenon was transitory it was evident that it could not be due to fibrosis. It was best observed in the right upper lobe. Tuberculous changes in the tracheobronchial lymph nodes produced progressive diminution in the size of the right upper lobe with upward displacement of the interlobar fissure. In a certain percentage of cases the further course showed development of obstructive atelectasis with all the characteristic clinical and roentgenological signs. However, in the 29 cases with shrinkage of the right upper lobe, only 10 per cent developed obstructive atelectasis. The other cases showed only what the author calls lobar hypoventilation. The X-ray signs of this condition are: progressive upward displacement of the interlobar fissure, especially in its lateral parts, up to the level of the second rib or the first intercostal space; upward displacement of the upper pole of the hilum. No displacement of the organs of the mediastinum was noted. There was a slight diminution in transparence

only with very marked contraction of the lobe. There was a lowering of the ribs as compared to the contralateral side. With regression of the specific inflammatory changes in the lymph nodes and reestablishment of normal bronchial patency all these changes were reversed. Thus, in 87 per cent a downward displacement of the interlobar fissure was observed. Only in cases with formation of pleural adhesions was the return to normal not noted. Hypoventilation of the other lobes were less clearly demonstrable. Hypoventilation of the whole lung has been observed mainly on the left side. There was a generalized diminution in transparence, a slight displacement of the heart to the affected side, upward displacement of the hilum and lowering of the ribs. In most cases of lobar hypoventilation the remaining lobes, and later on the contralateral lung, showed increased transparence, interpreted as transitory hyperventilatory emphysema.—*The Phenomenon of Pulmonary Hypoventilation in Tuberculosis of the Bronchial Lymph Nodes*, A. K. Prozorov, *Probl. tuberk.*, 1945, 1: 13.—(V. Leites)

**Laryngeal Tuberculosis.**—Laryngeal tuberculosis often proves to be fatal not because of the anatomical lesion but because painful dysphagia leads to starvation and death. The vast majority of such lesions has its anatomical basis in vasomotor disturbances around a small chronic lesion. In such lesions infiltration of the stellate or of the thoracic ganglions with novocaine may prove beneficial, since the painful dysphagia may be eliminated and the nutritional state of the patient may subsequently be improved. This method was used in 16 cases since 1937 and favorable results are reported.—*Le traitement des laryngites tuberculeuses oedémateuses par l'infiltration novocainique des ganglions stellaire et thoraciques supérieurs*, H. Mollard, H. Maschas & M. Duret, *Rev. de la tuberc.*, 1942, No. 6/8, 7: 193.—(G. Simmons)

**Pathology of Tuberculous Pleurisy.**—Tuberculosis of the pleura is a local manifestation of a generalized dissemination, while tubereu-

lous pleurisy accompanies frequently the different phases of tuberculosis. The gross anatomical and histological features of the tuberculosis of the pleura are quite characteristic and are easily recognized as of tuberculous origin. In tuberculous pleurisy the inflammatory exudative process predominates; it is usually difficult to find definite evidence supporting its tuberculous origin. The presence of acid-fast bacilli in the pleural effusion, as well as careful histological study of numerous slides may reveal the definite tuberculous nature of the effusion. Tuberculosis of the pleura usually follows a pulmonary or lymphoglandular process or bone tuberculosis. The gross aspect of the lesions may be miliary or submiliary or coarsely nodular.—*Anatomia macro y microscopica de las pleuritis tuberculosas*, A. L. Mallo, Hoja tisiol., March, 1945, 5: 99.—(L. Molnar)

**Serofibrinous Pleurisy in Tuberculosis.**—Case histories of 2,163 and of 1,000 patients, of two services of a tuberculosis hospital, were reviewed with a view to study the relationship of pleural effusion to pulmonary tuberculosis. There were 29 cases in the first group and 40 cases in the second group of patients with pleurisy in their past history. In 8 cases of the former and in 4 cases of the latter the pulmonary involvement appeared simultaneously with the pleural effusion. In the great majority of the cases in both groups the clinical manifestations of the pulmonary tuberculosis appeared within two years after the pleurisy. The age of the patients was from 15 to 30 years in from 50 to 70 per cent of the cases. The revealing symptoms were hemoptysis and toxemic symptoms. The lung lesions following a pleurisy were of ulcerocaseous nature in 42 cases; of fibrotic character in 10; there were enlarged hilar shadows in 19, hematogenous nodular lesions in 8 cases. Extrapulmonary involvement was present, intestinal tuberculosis in 18 cases, laryngeal tuberculosis in 10 cases and single cases of different localization.—*La pleuresia serofibrinosa como primera manifestación de la tuberculosis del adulto*, R. Cetrangolo, Hoja tisiol., June, 1945, 5: 2.—(L. Molnar)

**Hydrothorax.**—Recurrent pleural effusions due to cardiac insufficiency may be extremely chronic. To relieve patients of dyspnea it may be necessary to remove large amounts of fluid at short intervals for months and years. Intravenous salyrgan fails to influence the hydrothorax even though it may otherwise produce good diuresis. When salyrgan is given into the pleural cavity directly, a greater and more prolonged diuretic effect is observed. This is due to the slower absorption of the drug from the pleural space, and due to the dilution of the agent with the effusion. In a case of a 71-year-old hypertensive cardiac, the problem of recurring hydrothorax was finally solved by the obliteration of the pleural space by quinine and urethane solution. Four injections of this solution resulted in a permanent symphysis of the pleural leaves. The patient was considerably improved following this procedure and the good result was maintained for some time.—*Hydrothorax récidivant*, M. Roch, P. Alphonse & R. Roch, *Schweiz. med. Wchsnschr.*, April 28, 1945, 75: 381.—(H. Marcus)

**Neuritis Secondary to Pleurisy.**—Two cases are presented in which paralysis of one nerve in the homolateral arm had become manifest shortly after the onset of the pleural effusion. *N. cubitalis* and *N. circumflex*, respectively, were involved. The literature on the subject is reviewed and several theoretical possibilities are advanced to explain the nature of this complication, but no satisfactory explanation has been arrived at.—*Névrites des pleurétiques*. (*Paralysie cubitale droite contemporaine d'une pleurésie séro-fibrineuse droite. Paralysie du circonflexe droit au decours d'un épanchement pleural droit*), S. Belbenoit, *Rev. de la tuberc.*, 1941, No. 7/8, 6: 451.—(G. Simmons)

**Sodium Citrate in Treatment of Pleural Effusions.**—Sodium citrate was injected intrapleurally in cases with pleural effusions in an attempt to prevent coagulation of the fluid and retard or prevent formation of pleural adhesions. Sodium citrate, 3.8 per cent, has proved to be efficacious; 5 cc. were injected every other day for two to three months in 44

patients with pneumothoraces of five to six years' standing. Small pleural effusions were present, but in 81 per cent of cases thus treated no pleural symphysis occurred. Of 25 cases of acute febrile pleural effusion recuperation without symphysis was obtained in 21 (84 per cent). The pneumothorax could be maintained and remained satisfactory. The following technique was used: during the acute febrile stage 5 cc. of sodium citrate were injected into the pleural space and the injection repeated a week later. After the acute stage of the pleurisy had passed, fluid was removed as often as it appeared to be indicated and at the conclusion of each aspiration more sodium citrate was injected. The aspirations were continued until the fluid formation had stopped. It is believed that such treatment cuts short the febrile period, decreases the total amount of fluid produced and prevents the formation of adhesions.—*Le citrate de soude moyen de lutte contre la symphyse pleurale*, M. A. Dussert, *Rev. de la tuberc.*, 1942, No. 3/5, 7: 155.—(G. Simmons)

**Pleurogastric Fistula.**—In rare instances chronic empyemata penetrate through the pleural cavity and the diaphragm into the stomach. Only a few cases have been reported in the literature to which the author adds 2. Factors favoring this occurrence seem to be a poor tissue resistance which interferes with healing tendencies, and also a chronic infection of a tuberculous nature. Clinically the condition can be recognized by a sour smelling empyema drainage and by severe inanition. Barium given by mouth may pass readily into the pleural cavity only when the patient is turned into various positions. The seriousness of the condition requires that all chronic fistulae should be explored thoroughly by contrast media and their full extent established so that they may be drained surgically early and thus complications be avoided. The debilitated condition of the patient usually precludes more than palliative surgery so that the prognosis of pleurogastric fistula is almost uniformly bad.—*Pleurogastrische Fistel als Komplikation des Pleura-*

*empyems*, V. Kafka, *Schweiz. med. Wchnschr.*, June 9, 1945, 75: 520.—(H. Marcus)

**Tuberculous Pericarditis.**—The electrocardiographic changes in pericarditis are probably due to subepicardial myocarditis rather than the result of fluid accumulation in the pericardial sac. To substantiate this view, the author demonstrates tracings in a proved case of tuberculous pericarditis before aspiration, after aspiration and following air replacement, and several hours later following air absorption. The abnormalities consisted of an elevated arch shaped ST segment, most pronounced in lead II, and this change was present in all three tracings. Death occurred five days later from hemoptysis. Autopsy showed the presence of subepicardial myocardial involvement.—*Electrocardiographic Studies in a Case of Serous Tuberculous Pericarditis, in the Initial Stage*, L. E. Warfvinge, *Acta med. Scandinav.*, December 22, 1944, 119: 461.—(H. Marcus)

**Nasal Tuberculosis.**—A 25 year old female started in good health to have an acute coryza which was followed after five days by complete aphonia. Bilateral tuberculous lesions were found and bilateral pneumothorax was established, whereupon the aphonia disappeared. Two years later the patient had an epistaxis which was followed by painful swelling of the nose. Cauterization did not help and the dorsum of the nose started sinking in. A biopsy was done and a sessile tumor was found which had perforated the nasal cartilages and the septum and corroded the bone. The histological findings showed a vascularized tumor with infiltration of polynuclear and giant cells surrounded by epithelioid cells and lymphocytes. Small foci of necrosis were found. No tubercle bacilli could be seen in any of the slides. The diagnosis was tuberculoma. These tuberculomata are very rare, not more than 2 per cent of all tumors of the nose. They are more frequent in women than in men (4:1), most frequent in the age group of 20 to 40 years. The implantation in the nasal region results from traumatism, gen-



erally made by the finger. They have the tendency to invade and destroy the surrounding tissue. The first symptom is a unilateral progressive nasal obstruction with typical neuralgic pain, generally accompanied by epistaxis. The evolution is slow. The differential diagnosis has to consider malignancy, especially sarcoma, also papilloma, adenoma, epithelioma, and polyp.—*Tuberculosis nasal, forma pseudopapilomatosa del tuberculoma*, J. A. Sciuto, J. C. & H. C. Alonso, *Rev. de tuberc. d. Uruguay*, 1944, 12: 253.—(W. Swienty)

#### Osteo-articular Tuberculosis in Childhood.

—The incidence of osteo-articular tuberculosis in children is high in Lima, Peru: in two years 156 cases were diagnosed on the Orthopedic Service of that city. In 53.59 per cent of these cases there was involvement of the spine, in 26.92 per cent of the knee, in 23.78 per cent of the hip, in 3.86 per cent there was osteoarthritis of the foot; besides one case of each: hand, elbow and sacrum, was observed. The age of the patients ranged from one year to 13 years. The largest incidence was shown by the age group from 5 to 10 years (46.25 per cent), followed by the age group from 2 to 5 years (32.69 per cent); 63.46 per cent of the patients were males and 36.54 per cent were females. No apparent reason could be invoked to explain the higher incidence of the disease in males. It is significant that more than half of the patients attended the clinic for the first time more than six months after the onset of clinical symptoms. Local traumatism was almost always present in the history of the patients. The presence of abscess, discharging sinuses, luxations and subluxations complicated the picture in 42.95 per cent of the cases. Owing to deficiency in equipment and to lack of funds, only one part of the cases were studied by X-ray: in 62 cases where chest X-ray was taken there were lung infiltrations in 70.92 per cent and enlarged hilar shadows in 11.29 per cent. Only 20 children could be hospitalized, while the remainder of the children received only ambulatory treatment. The above data reveal the severe deficiency in the care of these patients that calls

for urgent measures to facilitate the early diagnosis and the proper treatment in specialized hospitals.—*La tuberculosis osteo-articular en la infancia*, R. Tijera, *Rev. méd. peruana*, March, 1945, 18: 195.—(L. Molnar)

**Ileocecal Tuberculosis.**—Ileocecal tuberculosis requires X-ray confirmation. The finding of inflammatory lesions in the ileocecal region in a tuberculous patient is good presumptive evidence. The X-ray task, therefore, is to determine whether organic inflammatory disease is present. In a tuberculosis hospital the problem is a little simpler than in the random case of a general hospital. There is a wide variation in the clinical signs and symptoms; indeed, a patient may have extensive disease with few or no gastro-intestinal symptoms. However, X-ray findings are sufficiently constant to indicate the real diagnosis. Pain is usually greatest in the right lower quadrant and generally is accompanied by tenderness about McBurney's point. Occasionally tumefaction is present, and attacks may suggest transient volvulus or acute appendicitis. Diarrhea may be present with or without positive stool cultures. Direct roentgenological evidence is looked for in the terminal ileum, ileocecal valve or cecum, while indirect evidence is given by the remainder of the ileum, appendix and colon. The *poas* shadow is also of importance. An enlarged spleen or liver due to amyloid can be seen on abdominal X-ray films. The examination includes hourly studies of the small intestine until the ileocecal region is clearly visualized. Barium enema studies are also made. Here the postevacuation films may be the most informative. The terminal centimeters of the ileum are the most frequently involved. Simple transient spasm may characterize early disease, and there may also be a slight mucosal irregularity. In later disease loss of mucosal markings may be accompanied by narrowing of the terminal ileum which often is associated with irregularity of the walls, straightening and rigidity of the walls and a cone-shaped terminal ileum, or a string-like appearance of the ileum. Loss of normal changes in ap-

pearance on serial exposures and possibly an ulcer crater may also be noted. In the region of the ileocecal valve the most common X-ray findings are increased visibility of the valve, a gaping of the valve with no evidence of obstruction, delay or obstruction at the valve and regurgitation of medium when the barium enema is evacuated. The appearance in the region of the cecum also depends upon the duration and severity of the lesion. Here one may observe mucosal irregularities, spasm and deformity of the usual cecal shape, stiffening in contour of the cecum, Stierlin's sign and a negative shadow caused by the ileocecal valve. Indirect roentgenological signs include irregularity in contour, evidence of ulcer or fixation of the appendiceal outline, a segmented and fragmented appearance of the colon and ileum, obliteration or poor visualization of the psoas shadow, evidence of an enlarged liver and spleen and disturbances in intestinal mobility.—*Ileocecal Tuberculosis*, M. R. Camiel, *Radiology*, April, 1945, 44: 344.—(G. F. Mitchell)

**X-ray Studies in Intestinal Tuberculosis.**—Tuberculous lesions of the intestine are classified as primary and secondary. The primary form is characterized by hyperplasia and involves in 76 per cent the cecum and the ascending colon. The secondary form can be either purely ulcero-exudative or hyperplastic. Serial X-ray films show that 30 per cent of all lesions are found in the terminal ileum, in the region of the ileocecal valve or in the first portion of the ascending colon. There may be nontuberculous inflammatory processes in the rest of the colon. The lesions are found in Peyer's patches. In some cases they heal by calcification. The rapidity with which the opaque material passes through the small bowel depends on the secondary irritation of the nerve endings and on the hyperdistension of the intestinal lumen. There may be incomplete obstruction and modifications in the calibre of the loops with hypermotility or, in the more chronic forms, sensation of peristalsis. The most important sign is gas formation. Alternating zones of distension with

almost filiform obstructions may be found. In the large intestine there is hyperperistalsis in the ulcerative and distension in the sclerotic forms. The colon may lose completely its mucous and muscular pattern and be seen as a rigid tube. In the hyperplastic form the lumen of the colon may be partially obstructed and the X-ray picture may be that of a tumor. The localized form of secondary intestinal tuberculosis is most frequent (80 to 90 per cent) in the region of the ileocecal valve. There may be generalized or solitary ulcerations. The ileocecal valve is rigid. The rest of the colon may be intact or may show changes due to irritation. Fibrotic changes are generally late consequences, secondary to pulmonary tuberculosis. The diagnosis of tuberculous appendicitis can only be made by anatomico-pathological studies. The differential diagnosis of intestinal tuberculosis has to take into consideration: intestinal obstruction, amebic or ulcerous colitis, tumors, especially carcinoma, acute enteritis, ileitis, appendicitis, abscess, syphilitic lesions. A final diagnosis cannot be made by X-ray examinations alone, without pathological studies and laboratory tests.—*Radiologia de la tuberculosis enterocolo-peritoneal*, A. P. Heudtlass, P. A. Crocchi & J. A. Marti, *Prensa méd. argent.*, July 6, 1945, 32: 1261.—(W. Swienty)

**Genital Tuberculosis.**—A chronic ulceration of the vulva may be due to syphilis, leprosy, a neoplasm or tuberculosis, and the diagnosis can be made only by biopsy. However, if biopsy reveals giant cells or epithelioid cells only and no bacilli, animal inoculation is necessary. In the case presented the 33 year old woman had had a pleurisy ten years prior to the onset of the genital ulcer. The ulcer was found on the internal surface of the right *labium minus*. It was irregular with an ill-defined border. It was covered with a whitish membrane and presented granulations which bled easily. There was a small fistular tract extending toward the perineum. The patient had been under medical treatment for seven years. The lesion was removed with a thermocautery. Microscopic examination revealed the presence

of giant and epithelioid cells. Guinea pig inoculation was not done.—*Chronisches Vulvageschwür tuberkulösen Ursprungs, Z. E. Navratil, Zentralbl. f. Gynäk., 1941, No. 19, 65: 884.*—(G. Simmons)

**Tuberculous Tonsils and Cervical Lymph Nodes.**—From time to time reports have appeared to the effect that tonsillectomy had a favorable influence on the course of tuberculous lymphadenitis of the neck. It was felt that convalescence from the disease was more rapid and recurrences less common after tonsillectomy. On the basis of 47 cases observed in a children's sanatorium, the author concludes that recurrences and breakdown of cervical lymph nodes are just as frequent after tonsillectomy as before. If the removed tonsils were not tuberculous on histological examination, however, nonspecific lymphadenitis was less likely to recur. Of the 47 cases observed, tuberculous tonsils were found in 34 cases. The remainder of the patients showed nonspecific inflammatory changes in conjunction with tuberculous cervical lymph nodes. It is questionable whether the tuberculous tonsil and the tuberculous cervical lymph nodes constitute a primary tuberculous complex.—*Tonsillektomie und tuberkulöse Halslymphome, H. Wissler, Schweiz. med. Wchnschr., October 20, 1945, 75: 927.*—(H. Marcus)

**Skin Tuberculosis.**—Thirty cases of skin tuberculosis and related conditions were investigated as to the presence of tubercle bacilli in the lesions. Crushed biopsy material was injected subcutaneously in guinea pigs and simultaneously grown on specific media. The culture media employed were those of Löwenstein and Laporte (serum, egg-yolk, 5 per cent glycerine). Intracutaneous tuberculin tests were performed in all inoculated guinea pigs, starting three weeks after inoculation, and repeated at regular intervals if negative. The animals were killed after four to six weeks. The type and virulence of the isolated bacilli were determined as follows: (1) intravenous inoculation of rabbits with a dose of 0.01 mg., (2) intracerebral inoculation

of rabbits with a dose of 0.05 mg., (3) subcutaneous inoculation of guinea pigs with 0.01 mg. The intracerebral inoculation proved to be more effective than the intravenous in differentiation of bovine and human types. The virulence was evaluated according to the extent of lesions produced with a dose of 0.01 mg. in the guinea pig two months after inoculation. Virulent bacilli produced after this period of time serious disease in guinea pigs with extensive lesions in all organs. After inoculation with bacilli of low virulence the animals remained in good condition and presented only minimal lesions on autopsy. Among the 30 cases of this study 17 belonged to the group of tuberculosis of the skin: 5 cases of *tuberculosis verrucosa*, 6 cases of lupus, one case of tuberculous ulcer, 3 cases of ulcerated tuberculoma, 2 cases of inoculation with tuberculosis from without (one case of primary infection and one case of reinfection). In 16 out of these 17 cases tubercle bacilli could be demonstrated with the above described methods. Six other cases were considered belonging to the group of tuberculids, ("acnitis" of Barthelemy, ulcerated tuberculid, *erythema induratum*, Boeck's sarcoid). Only one positive inoculation result was found in this group; an attenuated human strain was isolated from the case of *erythema induratum*. All other cases of this group were found negative. The last 7 cases included skin lesions, the tuberculous nature of which is still unsettled (*granuloma annulare*, *lupus erythematosus*, acne). Only one positive inoculation was found in a case of *acne conglobata*, consisting of an attenuated human strain. The 6 other cases were negative. A total of 18 strains of tubercle bacilli were isolated; 15 were of the human type, 3 of the bovine type. Two bovine strains were of normal virulence, the third was slightly attenuated. Among the human strains 7 had normal and 6 attenuated virulence. No correlation was found between the age of the lesion and low virulence of the bacilli. However, the quantity of bacilli was greater in more recent lesions. Histological examinations were performed of all above enumerated lesions. The typical histological

pattern of tuberculosis was found in all cases of *tuberculosis verrucosa*, in 5 cases of lupus, in one case of tuberculous ulcer, and in one case of ulcerated tuberculoma. All these cases were confirmed as tuberculous by bacteriological examination. In 3 cases the bacilli could be directly demonstrated on the slides. It is believed that in some cases the histological aspect of a skin lesion is sufficiently typical to permit a diagnosis of tuberculosis even if tubercle bacilli are not demonstrable with the available methods.—*Le controle histobactériologique des tuberculoses cutanées*, F. Bloch & M. Ducourtieux, *Ann. Inst. Pasteur*, August, 1940, 65: 67.—(V. Leites)

**Pharmacological Action on Bronchi and Intrapleural Pressure.**—Drugs acting on the bronchial musculature were investigated regarding their effect on pulmonary volume and intrapleural pressures. The following substances were studied: adrenaline, ephedrine, atropine, acetylcholine, pilocarpine, eserine, yohimbine, ergotamine, histamine and substances of the nicotinic group. These drugs were administered to dogs in various doses intravenously, intrapleurally or subcutaneously. The animals were under chloral narcosis. The respiration was registered with a pneumograph, the intrapleural pressure was measured with a water-manometer. It was found that bronchodilating agents produced an increase in pulmonary volume with a concomitant fall in intrapleural pressure (in the sense of an increase in negativity). Bronchoconstricting agents had the opposite effect. The intensity of the action on pulmonary volume and intrapleural pressure varied with the dose of the drug. Small doses did not modify the pneumogram, a fact which is interpreted as absence of effect on the respiratory centre. The variations in volume and intrapleural pressure are considered due to action on vascular and bronchial musculature in the lung. With large doses the action was not limited to the lung, but affected also the respiratory centre, as evidenced by changes in amplitude, frequency, and sometimes even rhythm of respiration. Another mechanism

of the action on intrapleural pressure was considered (reference is here made to the studies of Brill, Prinzmetall, and Leake in U. S. A. on a similar subject): bronchoconstriction produces a resistance to the passage of air from and to the alveoli. This in its turn is thought to increase the carbon dioxide tension in the alveoli and in the blood. The result is stimulation of the respiratory centre with increase of inspiratory movements leading to the development of a more negative intrapleural pressure. Inversely, bronchodilating agents produce higher intrapleural pressures through relative depression of the respiratory centre and diminution of inspiratory activity.—*Mécanisme d'action des drogues bronchomotrices sur la pression intrapleurale*, J. Troisier, M. Baritty & D. Kohler, *Rev. de la tuberc.*, 1939-40, 5: No. 13, 1473.—(V. Leites)

**Respiratory Variations and Arterial Pressure.**—The authors have studied the influence of the respiratory variations on the arterial pressure in both the pulmonary and systemic blood circulations. Adult cats were studied with open thorax, with closed thorax and without opening the thorax but exposing the heart. The manometric readings were taken in the intrapericardial portion of the pulmonary artery, in the arch of the aorta and in the abdominal aorta. The changes in the arterial pressure in the systemic and pulmonary circuit depend on the type of respiration. There are fundamental differences between normal and artificial breathing. With normal breathing the pressure falls during inspiration in both circuits. It is delayed for two or three beats in the systemic circulation. The lowering of the intrathoracic pressure in inspiration increases the capacity of the vascular bed of the pulmonary vessels. The lowering of the pressure in the pulmonary arteries causes a diminished blood flow to the left ventricle which in return with some delay causes an inspiratory fall of the pressure in the systemic circulation. With artificial respiration the problem is different. In the authors' experiences, the pulmonary pressure rises both

in systole and diastole, and the systemic pressure falls during inflation especially when it comes to a state of filling which is nearest to normal respiration. This is due to an increase of the resistance in the pulmonary circulation. In addition, in artificial respiration with high hyperpressure the flow of the blood to both ventricles is impeded. This causes a fall of the systemic pressure and a reduced pulse pressure in both circulations. The difference was 6 mm. in the pulmonary circuit when the artificial hyperpressure was 30 mm. Hg. With equal intratracheal pressures a greater decrease of the pressure is obtained with closed thorax than with open thorax. The compression of the heart and of the great vessels by the intrathoracic pressure in closed thorax is responsible for this difference. The difference is small because the diastolic pressure in the pulmonary artery cannot be less than the intrapulmonary pressure. In moderate artificial respiration the fall of the pressure in the aorta is due to the difficulty of the circulation in the pulmonary bed. In hyperpressure the similarity in both circulations indicates the difficulty in the afflux of the blood to both ventricles.—*Mecanismo de las variaciones respiratorias de la presión arterial en ambos circuitos*, A. Lanari, V. A. Alberti & R. Gonzalez S., *An. Cáted. de pat. y clin. tuberc.*, June 1, 1944, 5: 28.—(W. Sirently)

**Influence of Sex Hormones on Pulmonary Tuberculosis.**—Administration of folliculine eliminates menstrual flairs-ups only in a certain percentage of cases, those with hyposecretion of folliculine. In cases with hypersecretion the administration of progesterone and especially testosterone gave excellent results by influencing favorably menstrual and premenstrual disturbances: congestion of the breasts, uterine pain, premenstrual hemoptyses, chest pain, febrile episodes and exudative extension of the lung lesions. On the other hand, in some cases testosterone has produced hemoptyses and congestive flairs-ups, which subsequently could be influenced by folliculine. It is therefore assumed that two modifications of the soil are unfavorable for

tuberculosis: hypersecretion and hyposecretion of folliculine. The following observation also corroborates this opinion: some patients have been at first improved by the administration of a hormone and then made worse by prolonging the treatment. The administration of the antagonistic hormone, which had been ineffective at first, was at this time very useful, at least for a short period.—*Une démonstration expérimentale de l'action du terrain sur l'évolution de la tuberculose pulmonaire*, H. Mollard & M. Durcl, *Rev. de la tuberc.*, January-February, 1944, 6: 41.—(V. Leites)

**Significance of Tuberculin Allergy.**—The variations of tuberculin allergy can be studied by following the same individual for a long period of time or by determining tuberculin sensitivity with quantitative precision in a great number of individuals of all age groups. The latter method was chosen for this study. The intracutaneous tuberculin test was performed on 941 subjects between the ages of 15 and 96, all free of clinical tuberculosis. Dilutions of 1:1000 and 1:100 were used. The following findings were noted: there was a progressive increase in the intensity of tuberculin reactions until the age of 30 or 40, a persistence at this level for a long period of time and a decrease in intensity during old age. The intensity of tuberculin reactions was evaluated under two aspects: first, according to the percentage of cases reacting to dilutions of 1:1000 (or 1:10,000) as compared to those reacting to 1:100; second, according to the percentage of strong, moderate or slight reactions with the weakest solution used. The intensification of the tuberculin reaction with advancing age cannot be explained in connection with primary infection. It is true that tuberculin allergy consecutive to primary infection increases in intensity for a certain time, but this time is short and usually does not exceed six to eight weeks, the maximum period being five months. Thus, tuberculin allergy due to primary infection reaches its height early. If the above findings indicate progressive intensification throughout the years, there must be a factor responsible which

counteracts the natural decline of allergy. This factor is considered to be the occurrence of exogenous reinfections. The influence of age intervenes also, in the sense that the general tendency to sensitizations increases as compared to childhood. Nonspecific sensitizations may furthermore stimulate tuberculin reactivity. The decline of tuberculin allergy during old age is considered due to diminished activity and more retired way of life, implying a constant decrease of chances of exogenous reinfection. A support for this view is seen in the fact that in experimental tuberculosis in animals no intensification of the tuberculin reaction is noted. This is attributed to the lack of exogenous reinfections under laboratory conditions. A further argument in favor of the above expressed theory is seen in the statistics of Opie and McPhedran, demonstrating higher intensity of tuberculin reactions in groups of individuals exposed to tuberculosis as compared to nonexposed groups.—*Données nouvelles sur l'évolution et la signification de l'allergie tuberculinique. Premier mémoire: les grandes tendances évolutives de l'allergie tuberculinique chez les sujets non-tuberculeux. Allergie et reinfection, G. Canetti & H. Lacaze, Ann. Inst. Pasteur, December, 1940, 65: 455.*—(V. Leites)

**Hypersensitivity and Immunity.**—The immunizing effect of  $R_1$  strain tubercle bacilli was studied under various aspects. In the first series of experiments vaccination was performed by subcutaneous administration. (1) Guinea pigs were infected with  $R_1$  strain bacilli in one to three doses of 1 to 1.5 mg. Six weeks later the animals were inoculated subcutaneously with small doses of moderately virulent bovine bacilli. With the exception of 2 animals, which presented rather numerous visceral lesions, all other animals had only inguinal and lumbar adenopathies and some tubercles in the spleen. All controls presented massive parenchymatous lesions. (2) Similar results were obtained with inoculation of moderately virulent human bacilli. (3) Intraperitoneal injection of moderately virulent human bacilli was performed six weeks after

vaccination with 2 mg. of  $R_1$  strain. Up to the fourth month after inoculation the animals showed granulations of the epiploon and lumbar and mesenteric adenopathies. Animals killed after the seventh month showed lesions in spleen, liver and lungs. The controls died with far advanced lesions within three to nine weeks after the virulent infection. (4) Inoculation of bovine bacilli of high virulence consecutive to vaccination with  $R_1$  resulted in death of 2 guinea pigs with caseous inguinal and lumbar adenopathies. The 4 other infected animals died fifteen weeks after inoculation with extensive visceral lesions. The controls died of generalized tuberculosis within eight to ten weeks. (5) Intraperitoneal infection with a very virulent bovine strain resulted in death with massive lesions in the organs nine to eighteen weeks later. Controls died within eleven to fourteen weeks. (6) Intracutaneous inoculation with a moderately virulent bovine bacillus produced twenty-four hours later a nodule, which subsequently went on to enlargement, central necrosis and ulceration within the next two months, after which time regression and scar formation were noted. The animals died or were killed between the fourth and seventh month. Massive adenopathies and some disseminated tubercles were found in the spleen and in the lungs. Controls developed the nodule at the site of inoculation only after twelve days. There also was subsequent enlargement and ulceration of the nodule, but no regression took place until the death of the animal. (7) Intracutaneous infection with very virulent bacilli after previous vaccination also resulted in an accelerated reaction. Fifty per cent of the animals died after eighteen to twenty-six weeks. Controls died after nine to thirteen weeks. Further experiments were performed in varying the route of the vaccinating injection. It was found that intravenous and intracutaneous vaccination gave the best immunizing results. Studies were made to determine the minimum time between vaccination with  $R_1$  strain and the first appearance of resistance against virulent infection. It was found that the immunity became manifest

between the fourteenth and the twenty-fifth day, remaining stationary up to the fifty-sixth day. It is concluded from all above experiments that vaccination with  $R_1$  strain could in no instance confer a complete immunity to superinfections and had in the best case a retarding effect on the appearance and progression of lesions. The second part of the paper deals with the relation between tuberculin allergy and immunity. Guinea pigs were vaccinated with  $R_1$  bacilli and subsequently desensitized with repeated injections of tuberculin. Intracutaneous injection of virulent bovine bacilli was then performed. Two out of the fourteen guinea pigs presented no local reaction twenty-four hours after inoculation, whereas all vaccinated but not desensitized animals showed a local reaction twenty-four hours later. The vaccinated and desensitized guinea pigs began to show local reactions from the fifth day on, which had the typical characteristics of tubercles on the thirteenth day. In nonvaccinated controls the local reaction appeared on the ninth day. In the two groups of vaccinated animals (desensitized and non-desensitized) the further development of the infection was identical. It was retarded as compared to controls and finally led to death of generalized tuberculosis.—*L'hypersensibilité à la tuberculine et la résistance aux surinfections virulentes produites par le bacille tuberculeux atténué  $R_1$* , A. Boquet, *Ann. Inst. Pasteur*, January, 1941, 66: 32.—(V. Leites)

**Sympathetic Nerves and Tuberculin Reaction.**—Preliminary experimental data favor the conception that tuberculin skin reactions are secondary to an altered sensitivity of the neurovegetative system. Novocaine infiltration of the cervico-thoracic sympathetic system decreases the tuberculin response in the homolateral arm both as to size and redness of the reaction. Subsequent injections of novo-

caine prolong and reinforce this decrease of the tuberculin response; never, however, does the tuberculin test turn entirely negative. Injection of a stellate ganglion only is without effect, probably because not all the sympathetic nerve fibres of the upper extremity pass through it. Some may reach the first thoracic ganglion directly.—*Influence des infiltrations du sympathique sur les intradermo réaction a la tuberculine*, G. Guiot & J. D. Ghali, *Rev. de la tuberc.*, 1941, No. 5/6, 6: 521.—(G. Simmons)

**Nature of Tuberculin.**—The antigen-antibody reaction occurs not only *in vivo*, but also *in vitro*, and may be manifest by precipitation in test tubes. This enables more accurate studies to be made. The toxic reaction to Old Tuberculin in the tuberculous patient is an allergic phenomenon. The potency of Old Tuberculin is measured by ability to kill guinea pigs; due to a dialysable polysaccharide, or by skin reaction. This latter is caused by a non-dialysable substance, which may be precipitated by ammonium sulfate or trichloroacetic acid. The protein precipitated by the former chemical has a molecular weight of 32,000, whereas the latter has one of 16,000 and is non-antigenic. This pure protein derivative may be obtained from culture filtrates with much care and avoidance of heat. A union of the protein with a colloidal substance prevents antigenicity, but the ability to cause a skin reaction is retained. For standardization a tuberculin unit was defined as the active substance in 1/100,000 cc. of Old Tuberculin. In guinea pigs the sensitivity to tuberculin was directly proportional to the duration of infection with tuberculosis. Such a relation has not been shown in humans.—*Ueber Reindarstellung, Wirkungsmechanismus und Wertbemessung von Tuberkulin*, R. Prigge, *Schweiz. med. Wchnschr.*, January 20, 1945, 75: 63.—(J. Gerstein)

# MINIMAL TUBERCULOSIS IN THE NEGRO<sup>1,2</sup>

A Study of Negro Patients Discharged from Robert Koch Hospital  
with Minimal Tuberculosis between 1927 and 1942

SAMUEL S. ROMENDICK AND ADRIAN A. BONNER

In the past, tuberculosis in the Negro was considered by many prominent phthisiologists throughout the country as a rather fulminating disease. We, at the Robert Koch Hospital, have not been totally in accord with this concept for a number of years. As a matter of fact, of late, we have not been too fearful of minimal pulmonary tuberculosis in the colored. Therefore, it was felt that some definite knowledge of the end-results of Negroes discharged with minimal tuberculous lesions of the lungs would be of interest. We attempted a follow-up study of all Negro patients discharged from Robert Koch Hospital from 1927 to 1942 with a diagnosis of minimal pulmonary tuberculosis.

In choosing the material for this study, the records at Robert Koch Hospital of all minimal cases discharged from 1927 to 1942, inclusive, were reviewed. During this period, a total of 224 patients were discharged with minimal tuberculosis. Of this number, 65, or 29 per cent, were colored. Ordinarily, the patient population of the hospital consists of about 35 per cent Negroes.

In this latter group of 65 patients, 13 were eliminated for the following reasons: 4 cases were in the hospital less than three months; 3 had primary infection tuberculosis; 2 of them were children under 6 years of age; one died of extensive bone tuberculosis with multiple draining abscesses; and in 3 instances we were unable to obtain any adequate follow-up information. Thus, 52 cases were actually reviewed in this study.

## ANALYSIS OF DATA

*Deaths:* To depart from the usual form of such studies as this, we shall consider first the deaths. It is of great interest to note that in not a single one of our series was pulmonary tuberculosis the immediate nor even the contributory cause of death.

Of this group of 52 patients who have been out of the hospital for three to eighteen years, only 2, or approximately 3.9 per cent, died, one month and five years, respectively, after being discharged. One of the deaths was due to syphilis of the central nervous system. This occurred one month after the patient was transferred to another institution for further and more intensive antisyphilitic therapy (fever therapy). The other patient died five years after leaving this hospital from complications resulting from an automobile accident.

This death record becomes even more significant when we consider the time interval covered (three to eighteen years), the tendency of tuberculous families to migrate, and the reluctance of many people to report to clinics. In spite of

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<sup>2</sup> Read before the St. Louis Trudeau Club, June, 1945.



these facts, it still can be stated that 96.1 per cent of our Negroes with minimal pulmonary tuberculosis are living three to eighteen years after they were discharged from the hospital.

*Readmissions:* Ten, or about 19 per cent, of the cases reviewed were readmitted because of a reactivation of their disease. All readmissions occurred between three and thirty months following discharge. The average length of hospitalization at their previous admission was thirteen months. All cases were readmitted as moderately advanced, 7 to Robert Koch Hospital and 3 to other institutions.

*Sex and age:* There were 25 males and 27 females in this group. These figures

TABLE 1

*Negro patients discharged from Robert Koch Hospital between 1927 and 1942 classified by sex and age on admission*

AGES ON ADMISSION IN YEARS	ALL PATIENTS		MALE		FEMALE	
	Number	Per cent	Number	Per cent	Number	Per cent
6-9	3	5.8	1	4.0	2	7.4
10-19	11	21.1	5	20.0	6	22.2
20-29	19	36.5	7	28.0	12	40.7
30-39	13	25.0	7	28.0	6	22.2
40-50	6	11.5	5	20.0	1	7.4
Total.....	52	100.0	25	100.0	27	100.0

TABLE 2

*Negro patients discharged from Robert Koch Hospital between 1927 and 1942 Classified by marital status on admission*

MARITAL STATUS	ALL PATIENTS		MALE		FEMALE	
	Number	Per cent	Number	Per cent	Number	Per cent
Single.....	27	51.9	13	52.0	14	51.8
Married.....	21	40.4	10	40.0	11	40.7
Widowed, divorced or separated.....	4	7.7	2	8.0	2	7.4
Total.....	52	100.0	25	100.0	27	100.0

may appear somewhat unusual since it is claimed that sanatoria usually admit more men than women (1).

The females on admission were somewhat younger than the males. This is commonly true for the general population of most tuberculosis sanatoria. From table 1 it can be seen that in this series the mean age on admission for the females was 25 years, while that for the males was 29 years. However, for the total population at this hospital the difference in age on admission between the sexes is more pronounced than for this selected group.

*Marital status:* On admission to Robert Koch Hospital 40.4 per cent of the patients were married, 51.9 per cent single and 7.7 per cent widowed, divorced or separated as shown in table 2.

In this connection, it is of interest to note that of the 10 patients requiring re-hospitalization, only one was single. This is undoubtedly the result of the age factor rather than that of the marital status. Most of these single patients were in the younger groups. Another significant factor is that single persons tend to remain in the hospital longer, because they are usually confronted by fewer socio-economic problems. This is especially true of single women. Thus, it would appear that the tendency towards a longer period of hospitalization among the younger and single patients makes them better risks against reactivation of their disease after having been discharged from the hospital.

*Contact history:* Information regarding tuberculous contacts is usually unsatisfactory because the questioner often probes into this with insufficient care. Furthermore, in many instances the patient is not aware of the actual contact. In this study no contacts outside the immediate family were recorded. Twenty, or 36 per cent, of the 52 cases reviewed gave a family history of tuberculosis prior to admission.

An interesting side-light on the subject of family history is that in the follow-up examinations active tuberculosis was found in an additional five families. In 2 of these instances our patient had left the hospital before completing treatment. The remaining 3 patients, in whose families tuberculosis was later discovered, were discharged as arrested, but all 3 subsequently required readmission.

*Sputum:* According to recent studies, the relationship between tubercle bacilli in the sputum and the state of the disease is as follows: Two-thirds of the minimal cases, fewer than one-half of the moderately advanced and one-fifth of the far advanced cases are sputum-negative on entrance to the hospital (1).

Twenty-six, or 50 per cent, of the 52 cases in this study had a positive sputum on admission. Thus, the incidence of negative sputum in this study is much less than that given as the average for minimal cases throughout the country. The average for other hospitals is 66.7 per cent for both racial groups, while for the colored at Robert Koch Hospital only 50 per cent were sputum-negative. A very diligent search is made at our laboratory before considering the sputum negative.

*Associated diseases:* Almost 14, or 26.9 per cent, of the group under study had extrapulmonary tuberculosis. The various extrapulmonary lesions in their order of frequency were as follows: 5 had tuberculous perirectal abscess; 5 tuberculous spondylitis, 2 with psoas abscess; 3 tuberculous cervical adenitis; and one tuberculosis of the kidney. An additional 20, or 38.4 per cent, of the group had nontuberculous diseases which at the time of discharge presented a serious menace to their future health. These were 14 syphilitics, 3 with hypertensive-vascular diseases, 2 with gonorrheal salpingitis and one with diabetes. Only 18, or 34.6 per cent, of the entire group were discharged with pulmonary tuberculosis as the sole diagnosis. These figures present two interesting facts. First, not only were there no deaths among this last group, but also no readmissions to this or any other hospital for tuberculosis. Second, even though 65.4 per cent of the entire group had some other serious disease associated with tuberculosis, the over-all mortality for a period of three to eighteen years was only 3.9 per cent.

*Occupational history:* According to the records at Robert Koch Hospital, 37, or roughly 71 per cent, of the patients were gainfully employed prior to admis-

sion. Another 10, or 19.2 per cent, were students and 3, or 5.8 per cent, had no occupational history.

Unfortunately, the records of many of the patients listed but one occupation and too frequently no dates accompanied this information. In such instances the pursuit listed was accepted as the chief occupation before entrance to the hospital.

Six persons, or approximately 11.5 per cent, of the entire group studied were gainfully employed as "white collar" workers prior to admission. To this group, one might add the 2 housewives, who constitute an additional 3.9 per cent, to the cases. Thus, a total of 15.4 per cent of the cases studied were apparently sufficiently established to be independent of further educational or vocational training following discharge from the hospital. It is of interest to note that of this latter group (15.4 per cent of the series) only one required readmission to this hospital. Reactivation of the tuberculosis after discharge was limited almost exclusively to the group of manual workers; 90 per cent of the readmissions were among this latter group. Thus, if we were to diminish the hardships and hazards of manual labor for tuberculous ex-patients, approximately 85 per cent of our Negro patients would require some form of vocational training or guidance after leaving the institution.

*Treatment:* The type of therapy that patients with pulmonary tuberculosis receive varies considerably with the stage of the disease. According to the literature, 80 to 90 per cent of minimal cases are given only bed-rest (1). The findings in the group studied seem to bear out this fact. Forty-seven, or almost 90 per cent, of these received only bed-rest and symptomatic therapy while in the hospital. The remaining 10 per cent were first given bed-rest. It was only after these latter patients had shown signs of increase of their disease while on bed-rest that more intensive forms of therapy were decided on. Of the 5 patients who received other forms of treatment, 3 were given phrenic nerve operations and 2 pneumothorax.

*Length of stay in sanatorium:* According to the literature, two-thirds of the tuberculous patients remain in sanatoria for a period of one year or less, and 45 per cent stay less than six months (1). The tendency of most patients is to remain in sanatoria for as short a time as possible. From table 3 it will be seen that the mean stay for these patients was about fourteen months. These data are even more significant when one realizes that the figures given in the literature represent hospital stay for all stages of the disease. Our figures, representing only minimal cases, show that only 15.5 per cent stayed for six months or less. Almost 40.4 per cent of the cases were hospitalized for one to two years. The other 17.3 per cent required longer periods of hospitalization because of some complicating factor, such as tuberculous spondylitis or tuberculous pleural effusion and other extrapulmonary tuberculous disease.

It is our opinion that this relatively long period of hospitalization is one of the significant factors in the obvious stability of the lesions in our cases. This is evidenced by the fact that after three to eighteen years no patients have died of pulmonary tuberculosis, and only 19.2 per cent required readmission because of

reactivation of their disease. Further evidence for this opinion is that 7 of the 10 readmitted patients were hospitalized initially for less than one year.

*Clinical status on discharge:* The clinical status of a patient at the time of discharge is an important factor in choosing candidates for rehabilitation. Fortunately, in this study, the majority, 35 patients, or 67 per cent, were discharged as arrested, and nearly 5.8 per cent as apparently arrested. The remaining 29 per cent were unstable and were discharged as either quiescent, improved or unimproved. These findings clearly show that the vast majority of these patients were suitable for vocational after-care, at least from a medical standpoint.

However, from the records it is not possible in all our cases to distinguish between those patients who left with the full advice of their physician from those whose departure was approved because of socio-economic conditions rather than purely medical reasons. Of the group studied, 41, or 78.9 per cent, were discharged with the approval of the hospital staff and 11, or 21.1 per cent, left of

TABLE 3

*Negro patients discharged from Robert Koch Hospital between 1927 and 1942*  
*Classified by length of stay in hospital*

LENGTH OF STAY IN MONTHS	NUMBER	PER CENT
0-5	7	13.5
6-11	15	28.8
12-17	15	28.8
18-23	6	11.5
24-29	7	13.5
30-35	0	0.0
36-41	1	1.9
Over 42	1	1.9
Total.....	52	100.0

their own volition. In this connection it is interesting to note that only 15 per cent of those who left with consent required readmission, whereas 40 per cent of those who left against advice subsequently were readmitted. It was stated in the recent literature that 23 per cent of all patients who left against advice were dead within five years (1). Our experience differs, undoubtedly because the cases dealt with were only minimal.

#### SUMMARY AND CONCLUSIONS

1. Of all patients with minimal pulmonary tuberculosis discharged from the Robert Koch Hospital between 1927 and 1942, 29 per cent were colored. (About 35 per cent of the patient population is Negro.)

2. Of the Negroes with minimal pulmonary tuberculosis, 96.1 per cent are living three to eighteen years after discharge.

3. In no instance was pulmonary tuberculosis the immediate or even a contributory cause of death.

4. The tendency towards a longer period of hospitalization among the younger and single patients accounts for fewer reactivations in this group.
5. Approximately 85 per cent of Negro patients require some form of vocational training or guidance after discharge.
6. Nine out of 10 readmitted patients were manual workers.
7. Thirty-six per cent of this series gave at least a family history of tuberculosis.
8. Fifty per cent of the series had positive sputum on admission.
9. There were 67.2 per cent of the cases discharged as arrested, 5.8 per cent as apparently arrested, and 29 per cent as unstable.
10. Of the group under study, 26.9 per cent had extrapulmonary tuberculosis.
11. And 38.4 per cent of the group had associated nontuberculous diseases.
12. Of the series, 34.6 per cent were discharged with pulmonary tuberculosis as the only diagnosis.
13. Ninety per cent of the cases reviewed received bed-rest as the sole form of treatment.
14. A longer period of hospitalization for minimal cases tends to give a greater stability after discharge; 7 out of 10 readmitted patients were initially hospitalized for less than one year.

#### SUMARIO Y CONCLUSIONES

1. De todos los enfermos con tuberculosis pulmonar mínima dados de alta en el Hospital Robert Koch, de 1927 a 1942, 29% eran de color. (Aproximadamente 35% de los enfermos hospitalizados son negros).
2. De los negros con tuberculosis pulmonar mínima, 96.1% viven de tres a 18 años después de dados de alta.
3. En ningún caso fué la tuberculosis pulmonar la causa inmediata o contribuyente de la muerte.
4. La tendencia hacia períodos de hospitalización más prolongados entre los enfermos más jóvenes y solteros, es la razón por la que hay menos reactivaciones en este grupo.
5. Aproximadamente 85% de los enfermos negros requieren cierta forma de preparación u orientación profesional después de dados de alta.
6. Nueve de 10 enfermos readmitidos eran obreros manuales.
7. De esta serie 65% dieron por lo menos una historia de tuberculosis familiar.
8. En 50% había esputos positivos a su ingreso.
9. A 67.2% de los casos se les dió de alta como estacionados; a 5.8% como aparentemente estacionados, y a 29% como inestables.
10. Del grupo en estudio, 26.9% tenían tuberculosis extrapulmonar.
11. Un 38.4% tenían otras enfermedades no tuberculosas.
12. A 34.6% se les dió de alta con tuberculosis pulmonar como único diagnóstico.
13. El 90% de los casos recibió reposo en cama como forma única de tratamiento.

14. En los casos mínimos, una hospitalización más prolongada suele producir mayor estabilidad después del alta; 7 de 10 reingresados fueron hospitalizados primitivamente por un período menor de un año.

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# A SIMPLE AND PRACTICAL METHOD OF OBTAINING COMPLETE BRONCHOGRAMS<sup>1</sup>

J. KARL POPPE<sup>2</sup>

With a more general recognition of the indications for pulmonary resections, an increased need for routine diagnostic bronchograms has developed during the past few years. Every patient with a chronic cough, and especially those with hemoptysis, in whom pulmonary tuberculosis is not evident on a plain chest film, should have a bronchogram. Bronchography is the only satisfactory method of diagnosing bronchiectasis and is extremely helpful in discovering an early bronchogenic carcinoma.

A simple, easy and time-saving method must be practised in order to make bronchography available to all patients who need it. A multitude of techniques have been recommended and are in use to-day throughout the country. Some of these methods are sufficiently intricate and time-consuming to require hospitalization and a highly specialized personnel even to attempt them. A method which requires bronchoscopic instillation of oil or intratracheal intubation definitely limits the application of bronchography. Complicated postures and special tables discourage many physicians from attempting bronchography. An incomplete bronchogram with only a minimal filling of one or two lobes is worthless from a diagnostic viewpoint. A complete filling of all of the major bronchi on both sides is necessary before considering a patient for a lobectomy in case of bronchiectasis.

The following method is offered for obtaining complete bilateral bronchograms on ambulatory patients on two X-ray films within a half hour. No claim is made for originality of this method. It is based largely on Singer's method described in 1926, but yet greatly modified. The only claim is simplicity and economy of money and time for both the patient and physician. A few details of the procedure which are enumerated and stressed make a tremendous difference between the successful filling of all the major bronchi and a worthless picture with only a few drops of oil scattered about the pulmonary parenchyma and stomach. The three fundamental principles for obtaining good bronchograms are: adequate anesthesia, avoidance of delay between the injection of the oil and taking the X-ray film, and maintaining constant traction on the tongue until the film has been taken.

## BRONCHOGRAPHIC PROCEDURE

1: Preparation of the patient for a bronchogram (desirable but not absolutely essential, except in young children and elderly debilitated adults):

A. Give nothing by mouth for two or three hours preceding the bronchogram to avoid vomiting.

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B. Give nembutal 0.1 gram two hours before the bronchogram.

1. Barbiturates act as a prophylactic and antidote for pontocaine (cocaine) poisoning.
2. Sedative action reduces apprehension, especially in young children who require the same adult doses to insure cooperation.

C. Postural drainage for one-half hour immediately preceding bronchograms.

1. This is especially valuable in cases of severe bronchiectasis.



FIG. 1

FIG. 1. Normal right posterior semi-oblique bronchogram clearly distinguishing all of the major bronchial divisions on one film.



FIG. 2

FIG. 2. Left posterior semi-oblique bronchogram showing extensive bronchiectasis involving the left lower lobe and the lingular division of the left upper lobe. Note the separation of the lingular division accomplished by the slight rotation of the patient to prevent its overlying the lower lobe shadow.

2. The bronchiectatic cavities must be emptied of pus before they can be filled with lipiodol.

D. Give codeine 0.065 gram fifteen minutes before a bronchogram to inhibit the cough reflex.

## 2: Anesthetization of pharynx and trachea:

- A. Use as a spray one full ounce (30 cc.) of freshly prepared 1 per cent pontocaine for all normal adults.

1. Pontocaine has less toxic effects than cocaine.



2. A dilute solution given slowly seems more effective and less toxic than a higher concentration.
3. A pontocaine solution deteriorates rapidly on standing.
- B. Hold out the patient's tongue to open the pharynx while spraying the throat.
- C. Have the patient breathe in and out through the mouth to permit anesthetization of the posterior pharynx, glottis and trachea.
- D. Continue spraying the pharynx slowly at frequent intervals over a fifteen to twenty minute period, until all the pontocaine solution has been used.
  1. Encourage the patient to cough up excess secretions between each period of spraying.
    - a. Do not permit him to swallow the pontocaine since rapid absorption of the drug in the stomach increases the danger of a toxic reaction.
    - b. Vigorous coughing assists in emptying the bronchiectatic cavities of pus and permits better filling with lipiodol.
  2. Consider the anesthesia complete only when the patient is unable to swallow.

### 3: The position of the patient for introduction of lipiodol:

- A. Have him sit on a stretcher in front of the fluoroscope.
- B. He should lean on the right or left elbow depending on which side is to be outlined at that time.
- C. Check the position with the fluoroscope before injecting the oil.

### 4: Introduction of lipiodol into the bronchi:

- A. Use 10 to 12 cc. of 40 per cent suspension of lipiodol for each side of the chest.
  1. The use of larger quantities than this floods the bronchi and spills over into the alveoli, obscuring the bronchial outline.
- B. Warm the lipiodol before using to reduce its viscosity.
- C. Grasp the patient's tongue firmly with a piece of gauze in the left hand and draw it out of the mouth at maximum extension.
  1. The patient will be unable to cough or swallow as long as firm traction is maintained on the tongue.
    - a. Extra traction is needed in case the patient attempts to swallow.
  2. Maintain this traction on the tongue until the X-ray picture has been completed.
- D. Have the patient breathe in and out in rapid respirations of normal depth (about 30 times a minute).
  1. Slow deep respirations permit an opportunity to cough and should be avoided.
  2. Very shallow respirations do not permit the oil to pass down through the glottis.
  3. The proper type of breathing may be described as similar to that of "a panting dog on a hot day."
  4. Any hesitation in breathing anticipates a paroxysm of coughing and should be discouraged.
- E. Slowly drip the lipiodol over the back of the tongue into the pharynx.
  1. Use a straight metal cannula attached to a 20 cc. syringe.
  2. Keep the chin tilted up and the head erect to prevent the oil from running out of the corner of the mouth.
  3. Hold the same position for thirty to sixty seconds after the injection to permit the pharynx to be emptied of oil.

- a. The cessation of gurgling in the throat indicates that all of the oil has finally run down into the trachea.

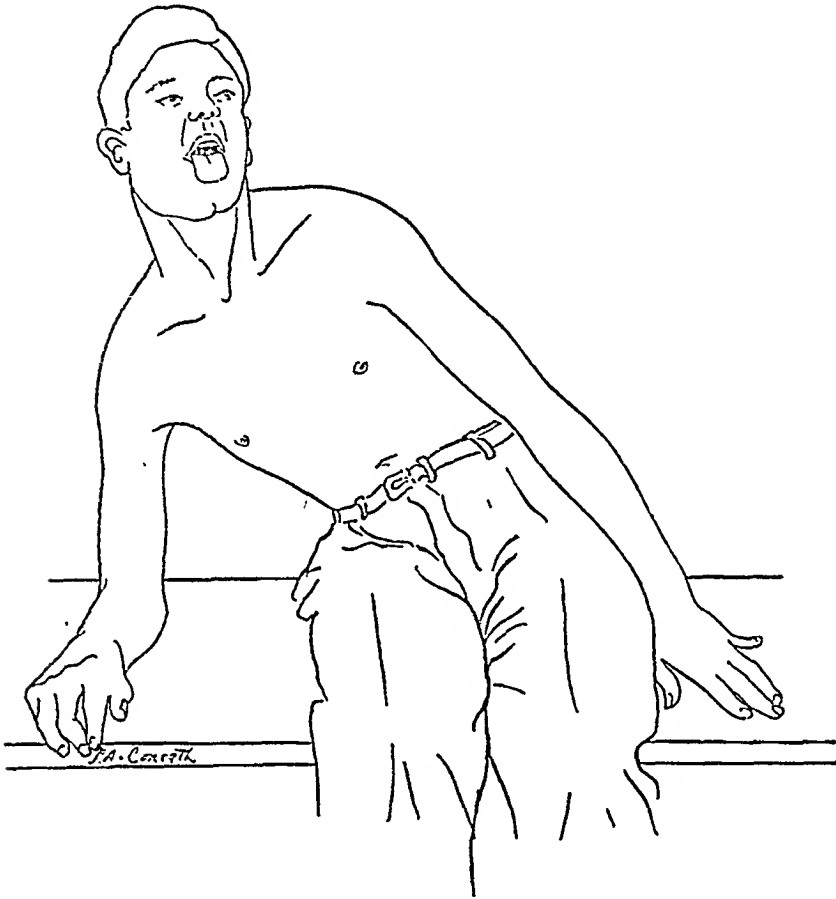


FIG. 3. Correct position of the patient on the stretcher in front of the fluoroscope for the introduction of the lipiodol into the right lung.

5: Check the bronchial filling immediately with the fluoroscope:

- A. Add more oil immediately in case the major bronchial divisions are not well outlined.
- B. Do not expose the film until satisfactory filling is obtained under the fluoroscope.
  - 1. Another attempt with heavier premedication may be required on the following day.

6: The best positions of the patient to fill all the major bronchi:

- A. Lay the patient down on the desired side on the stretcher.
  - 1. Roll him slightly forward to fill the middle lobe bronchus, if the right side is under consideration.
- B. Lift the foot of the stretcher to a 45° angle for about thirty seconds to fill the upper lobe bronchus.

7: The best positions for X-ray films (posterior semi-oblique position):

- A. Stand the patient up with his back to the cassette.
- B. Elevate the arm above the head on the side under consideration.
  1. This draws the scapula forward out of the way.
- C. Rotate the patient slightly so that one fist can be inserted between the cassette and the shoulder opposite the side under consideration.

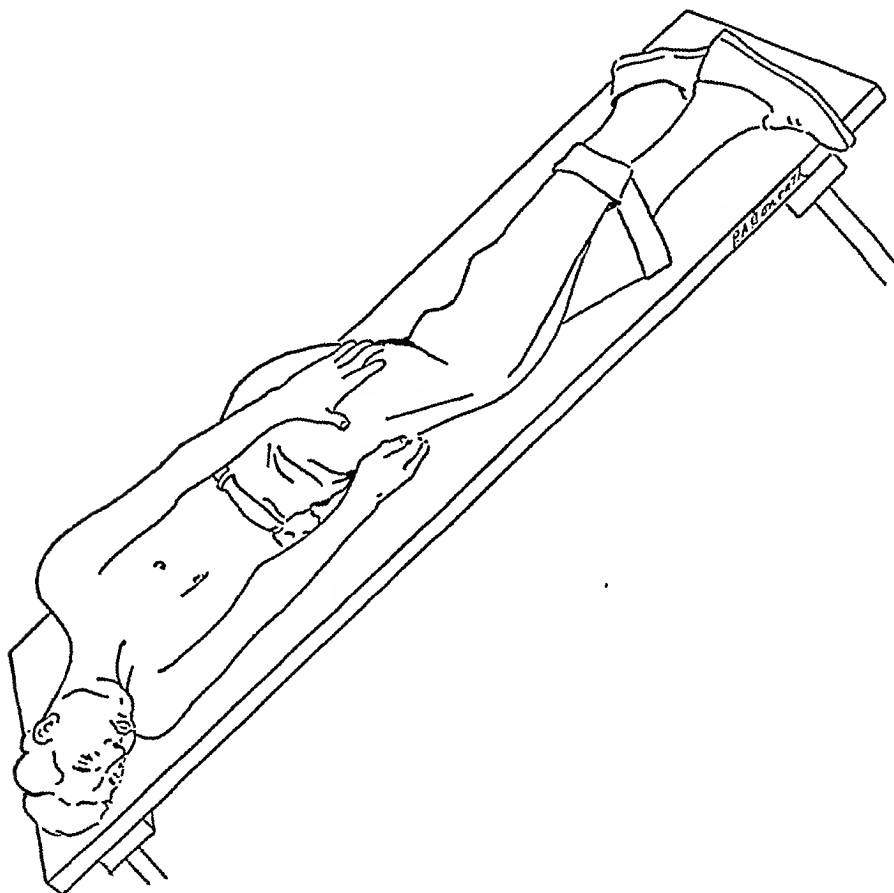


FIG. 4. The foot of the stretcher is elevated to a  $45^\circ$  angle and the patient rotated slightly forward to fill the right upper and middle lobe bronchi.

1. This slight rotation permits one to distinguish the right middle lobe bronchi or the lingular branch of the left upper lobe from the lower lobe bronchi.
  - a. No additional lateral film is necessary when this semi-oblique position is used.
2. A rotation of  $45^\circ$  or more should be avoided because it causes the cardiac silhouette to be superimposed over the bronchogram obscuring its details.

8: Special X-ray techniques required in particular cases:

- A. An over-exposed Bucky technique may be needed in cases with a dense opacity over one hemithorax.

1. This is frequently necessary in cases with a massive atelectasis or pneumonitis resulting from a bronchial obstruction.

#### 9: Bilateral bronchograms:

- A. The two sides may be filled in rapid succession under the same anesthesia.
  1. Only 10 to 12 cc. of lipiodol should be used on each side.
  2. The patient may expectorate but should be discouraged from coughing between the two bronchograms.

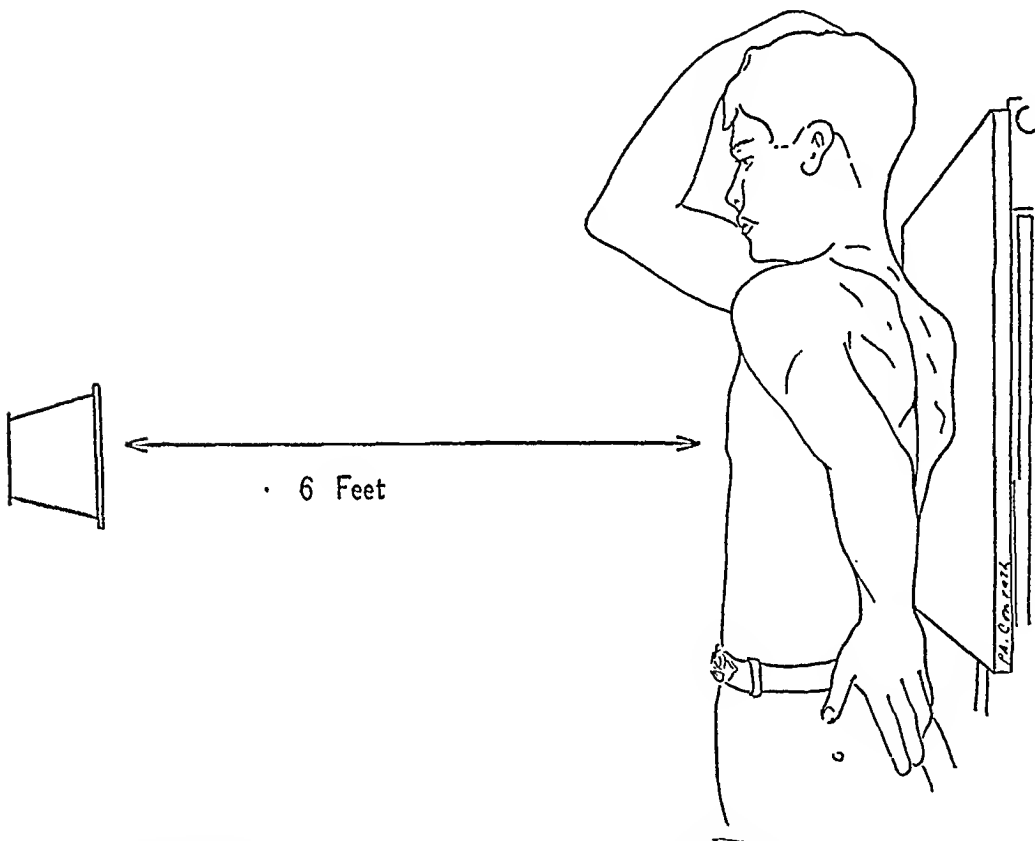


FIG. 5. Illustration of the right posterior semi-oblique position used for a right bronchogram.

#### 10: General consideration for a successful bronchogram:

- A. Adequate anesthetization of the pharynx and trachea.
- B. Completion of all preparations before injecting the oil.
  1. Notify the X-ray technician to have the cassette in place and properly labeled before starting.
- C. Move rapidly from one procedure to another so that the patient will not have an opportunity to cough up the oil before the X-ray picture is taken.
  1. The oil should be injected in front of the fluoroscope and in close proximity to the X-ray machine which will make the photograph.

## ADVANTAGES OF THIS METHOD OF BRONCHOGRAPHY

1. It can be performed on ambulatory out-patients.
2. Only one-half hour or less is required to complete a bilateral bronchogram. Three or four patients can be worked up in an hour by one person if they are anesthetized simultaneously.
3. No elaborate special equipment is required.
4. No complicated intratracheal techniques or elaborate postures are used.
5. A complete filling of all of the major bronchi is obtained under one anesthesia.
6. Only two chest films are required for accurate identification of all of the major bronchi on both sides of the chest.

# BRONCHOGRAPHY IN TUBERCULOSIS

## A Clinical Study

L. BRYCE BOYER,<sup>1, 2</sup>

During the past quarter of a century contrast bronchography has come to play an important rôle in the diagnosis of pulmonary and particularly bronchial diseases. Numerous investigators have adopted its use. However, there are few studies recorded in which contrast bronchography has been extensively used in patients with pulmonary tuberculosis. Several possible reasons for this apparent neglect will be subsequently discussed.

In this investigation opaque media were used for bronchography in 50 patients who had pulmonary tuberculosis. The method of selection was simple. All the women on the Stanford University Medical School Tuberculosis Service of the San Francisco Hospital during the first six months of 1943 were used, excluding only those who were too weak to withstand transportation via guerny from the ward to the radiology department and those who were moderately to severely febrile. In addition, a few men were used, chosen at random. Due to inaccessibility of some data, only 46 patients are represented in the figures and discussion below. It is apparent that patients with all degrees and types of pulmonary tuberculosis were used in this investigative procedure.

## METHOD

The patients were given  $1\frac{1}{2}$  grains of nembutal. The pharynxes were anesthetized with a spray composed of equal parts of 2 per cent pontocaine and 1:1000 epinephrine. The anesthetization of the intrathoracic airways was accomplished by injecting 2 cc. of the same solution between the vocal cords while the patient inspired. Occasionally a little greater volume of anesthetic was subsequently required. A moderately hard straight catheter, No. 12 or No. 14 French, was passed into the trachea via the intranasal route when possible, and only rarely *per os*. The patient was transported to the radiology department and there, under fluoroscopic vision with gravitational control, the contrast medium was used. An attempt was made to inject only the areas involved by the tuberculous infection as demonstrated teleoroentgenologically and the minimum amount of contrast medium was used which filled the bronchi so that they could be seen under the fluoroscope. In the case of iodized oil, the amount was about 10 cc. per lung and, when thorotrast was used, a little less was needed. As many lobes as were diseased were injected at the same seance.

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## REACTIONS TO CONTRAST AGENTS

It was necessary to do 55 separate instillations in the 46 patients.

Three injections were made with thorotrast in patients in whom bronchial stenosis was suspected, in the hope that this less viscid preparation would traverse the stenosis and demonstrate peripheral bronchial patterns. The 3 injections were followed by severe febrile reactions and marked malaise, persisting for three days in 2 instances and two days in the third.

In 52 instances iodized oil (iodochloral or lipiodol) was used. In one case there was a severe reaction, with acute dyspnea, duration ten hours, and subsequent increase in sputum production from her usual 2 to 8 ounces; the increase persisted for over a week. This patient, 16 years old, had far advanced bilateral fibrous disease with some caseation and marked emphysema.

In 4 instances moderate reactions occurred. In a woman of 73 who had bilateral fibrous disease and marked emphysema, moderate dyspnea persisted for about twelve hours and a febrile reaction of 100° F. lasted three days. Her cough was worse for a week; her sputum was scarcely increased. A second patient, age 38, with bilateral fibrous disease and extensive emphysema, had acute breathlessness and sweating, thready pulse and cyanosis for about five minutes after the lipiodol injection into her right upper lobe bronchus. Subsequent instillation into the left upper lobe bronchus caused no trouble. Two other emphysematic women, age 31 and 57, had cough and sputum increase which lasted about five days.

Seven patients complained of breathlessness transiently when the pontocaine was instilled intratracheally, increased cough and sputum for two or three days or had a postbronchographic temperature rise of one degree or less for two days.

The remaining patients had no reactions. There were no spreads of disease which could be definitely attributed to the procedure, although in one woman, an hypertonic dancer, age 30, active disease developed on the right side two months after injection of the left upper lobe which had been inactive for some months. This case cannot be clearly attributed to the bronchography because the patient signed herself out of the hospital a few days following the procedure and was behaving badly.

## SEX, AGE AND RACE OF PATIENTS

In this series are represented 42 women and 4 men. The youngest patient was 16 and the eldest 73. The age grouping in decades was as follows:

16 to 25 years—	14 patients
26 to 35 years—	16 patients
36 to 45 years—	6 patients
46 to 55 years—	7 patients
56 to 65 years—	2 patients
66 to 75 years—	1 patient

Investigated were 43 whites, one red (Cherokee), one yellow (Chinese), and one brown (Filipino). Of the whites, 8 were of Latin American extraction

(and thus had probably some red race blood), 5 were of Mediterranean lands (Italian and Greek), 25 were Germanic, one Slavonic and 4 French.

### RESULTS

There were 4 patients who had purely exudative disease. Of these, one proved to have bronchial stenosis and in none was bronchiectasis found.

Eleven patients with fibro-exudative disease presented 3 instances of bronchial narrowing alone, 3 of dilatation only and one displayed both conditions. In summation, 4 patients had stenosis, 4 bronchiectasis and 4 neither complication.

Thirty patients with fibrous tuberculosis are recorded. In 2 bronchial stenosis only was found. Nineteen patients presented bronchiectasis without proximal obstruction. Six had both conditions. Only 3 patients showed neither. Addition of the cases displaying both complications shows 8 with bronchial stenosis and 25 with bronchiectasis.

The overall lobar incidence of bronchial complications revealed: (a) Eight lobes with exudative disease were injected, of which one was stenotic and none were dilated. (b) Twenty fibro-exudative lobes received radiopaque injections, exhibiting 3 stenotic bronchi, 3 dilated bronchi and one with proximal narrowing and distal dilatation. Four, therefore, displayed bronchial stenosis, 4 bronchiectasis and 12 neither. (c) Fifty-six diseased lobes of patients with fibrous tuberculosis revealed 5 with bronchial stenosis only, 36 with dilatation alone, 4 with both conditions and 11 with neither. Combination of the instances in which the same lobes displayed both complications with those in which only one was delineated yields 9 lobes with stenotic bronchi and 40 with dilated bronchi.

The lobar distribution and incidence of occurrence of the bronchial complication are revealed by the following figures: The right upper lobe was injected and involved in 2 exudative cases, the bronchus being stenotic once. In 5 fibro-exudative lobes, stenoses were found twice and dilated once. In 19 fibrotic lobes, 3 stenoses were noted and 12 bronchiectases. In one case stenosis and dilatation were coexistent.

There were no cases with exudative disease in the middle lobe. The one fibro-exudative case showed dilatation. There were 2 fibrous middle lobes injected, and these presented neither dilatation nor narrowing.

The right lower lobe was once involved by an exudative process which showed no bronchial changes. The 2 fibro-exudative involvements presented one instance of dilatation. Seven fibrotic lobes were injected and 6 displayed dilatation.

Three instances of exudative tuberculosis of the left upper lobe were examined. No bronchial complications were demonstrated. Among 5 fibro-exudative lobes, 2 showed stenotic bronchi. Of 20 fibrotic lobes, 14 showed dilatations and 2 bronchial stenosis.

The left lower lobe was infected with an exudative process twice without demonstrated bronchial change. Of 4 fibro-exudative cases, one showed bronchial stenosis. In 9 fibrous lobes 7 showed dilatation and 2 presented narrowed bronchi. One case presented both phenomena.





FIG 1. (Upper left) A 38 year old woman who had had known tuberculosis for twenty years. During the years, pneumothorax, bronchoscopy, and bilateral apical thoracoplasty were ineffective. Bilateral upper lobe bronchiectasis ensued.

FIG 2. (Upper right) A 20 year old Cherokee housewife who had had left upper lobe cavitation four years previously. Pneumothorax was abandoned because of complicating empyema. The cavities closed. Positive sputum remained as the only symptom. Left upper lobar bronchiectasis persisted with closed empyema.

FIG 3. (Lower left) A 26 year old Italian housewife who had had known tuberculosis for four years. An original left upper lobar cavity apparently closed with thoracoplasty and patient became clinically well but for left upper lobar rales. A bronchiectatic pouch persisted in the left upper lobe.

FIG 4. (Lower right) A 33 year old French housewife, who had had progressive re-erudescant tuberculosis for ten years, developed eventually multiple left upper lobar cavities. Endography revealed left upper lobar bronchial stenosis.

## BRONCHOGRAPHIC RESULTS IN RELATION TO PREVIOUSLY DIAGNOSED BRONCHIAL DISEASE

Using the ordinary criteria of bronchial tuberculosis as outlined by Salkin, Cadden and Edson (1), 30 of these cases had been diagnosed as having diseased bronchi. In these 30, stenosis was demonstrated 11 times, once where it had not been suspected; bronchiectasis was found by contrast bronchography in 18 cases. Neither stenosis nor dilatation was elicited in 6 cases.

Bronchoscopy was performed on 15 of the patients in whom bronchial tuberculosis had been suspected. This procedure failed to demonstrate disease of the bronchi 4 times in which bronchography proved its presence and twice when it was suspected clinically.

It is to be noted that 16 cases had not been suspected to possess bronchial disease. In one, stenosis and in 8, bronchiectases were proved.

In other words, in the 30 who had previous diagnoses of tuberculous bronchitis, 36 per cent were proved to possess stenotic and 60 per cent to have enlarged bronchi. In the 16 whose bronchi were considered normal, 6 per cent were stenotic and 50 per cent were dilated.

In no case was the patient thought to have had nontuberculous bronchiectasis.

Of the bronchiectatic patients, 24 per cent had chronic sinus disease. Of the patients without dilatation of the bronchi, 35 per cent were so afflicted.

## PATIENTS IN WHOM THE FOCUS OF POSITIVE SPUTUM WAS REVEALED BY BRONCHOGRAPHY

In only one case was the source of sputum demonstrated by bronchography after other means had failed. This woman, a 20 year old Cherokee, had a stationary, left-sided, closed tuberculous empyema, duration six years, and no other pulmonary lesions demonstrable by X-ray. Endoscopy did not reveal any bronchial tuberculosis although sputum came from the left upper lobe bronchus. Lipiodol instillation into the left upper lobe showed a bronchiectatic pouch.

## RELATIONSHIP TO COLLAPSE THERAPY

No direct relationship could be demonstrated between stenosis, bronchiectasis and the collapse therapy used in the treatment of these patients. It became apparent after analysis that the coincidence of bronchiectasis and thoracoplasty depended not on the induced collapse but upon the fibrous type of tuberculous lesions that necessitated it.

## SYMPTOMATOLOGY OF STENOSIS AND BRONCHIECTASIS

*Wheezing:* This occurred in 19 cases. Of these, 9 had demonstrable stenosis and 12 had bronchiectasis. Four had neither.

*Unexplained positive sputum:* In only one case was unexplained positive sputum present; she had bronchiectasis.

*Atelectasis:* Eighteen patients had either lobar or lobular atelectasis. Sixteen cases had upper, 2 middle lobe and 5 lower lobe atelectases. In the 16 patients

with upper lobe collapse, 18 lobes were involved. Five lobes had stenotic bronchi, 2 of these had bronchiectasis beyond the stenosis. Seven lobes had bronchial dilatation. Eight lobes had no proved evidence of dilatation.

Two patients had atelectatic middle lobes. Neither had demonstrable stenosis or ectasis of the bronchi. Three patients had unilateral lower lobe collapse. All had bronchiectasis, marked, saccular, and in none was bronchial stenosis demonstrated.

*Tension cavity:* Tension cavities were present in 5 cases, representing 8 lobes. Three lobes presented neither delineated bronchiectasis nor proved stenosis, 3 showed both bronchiectasis and stenosis and 2 presented stenosis alone.

*Solid sputum:* There was no statistical correlation between the type of bronchial disease and the sputum production. In addition, the patients without demonstrated bronchial disease had no less sputum than those with stenosis or bronchiectasis, regardless of quantity or position.

*"Positive" versus "negative" sputum:* Bronchiectatic patients presented positive sputum in 25 cases and negative sputum 4 times. This is at direct variance with the findings of Salkin *et al.* (1) who state "bronchiectasis strangely occurred more frequently in the negative group." Stenosis was always associated with positive sputum.

Thorotrast completely failed to outline any area which iodized oil did not.

#### DISCUSSION

Since the advent of contrast bronchography by Jackson (2) in 1918, few important strides have been taken. All are modifications of the methods of Sicard and Forestier (3) and Armand-Delille and Moncrieff (4). Iodized oil in its various preparations now occupies an important phase in the diagnostic armamentarium of the chest specialist. This is true also of the phthisiologist. Nevertheless, its use in the diagnosis of tuberculosis is not extensive, by and large. There are several reasons. The most important are: first, statistics transposed from autopsy records can generally be applied, in a large sense, to living groups; second, the dangers have been propagandized; third, the retention of oil in the alveoli obscures future roentgenographic shadows of pulmonary developments.

*Anatomical considerations:* Karsner (5), speaking of bronchiectasis, says, "Local dilatations may be due to the retraction of fibrous connective tissue contiguous with the bronchi, and local destructive inflammations may extend from without into the wall with consequent weakening and dilatation." He also states "...bronchiectasis originates in an acute respiratory infection. This may involve bronchi as an ulcerative lesion, with destruction of muscle and elastic tissue of the bronchial wall and penetration of inflammation into the surrounding lung tissue. This is replaced by a granulation tissue, which in turn becomes fibrous tissue coextensive with the destroyed area.... Dilatation is often observed before there is any contraction of the fibrous tissue." MacCallum (6) contributes, "Many theories have been formulated to explain the distention of the bronchi, but in these, all are agreed upon one point only, that the infection

and inflammation which weaken the bronchial wall and destroy its elasticity are necessary factors." Neither Karsner nor MacCallum specifically mentions tuberculosis as antedating bronchiectasis. However, it is easy to apply the criteria given to the pathology of tuberculosis. Salkin, Cadden and Edson (1) in 125 autopsies found bronchiectasis in 36 per cent of their cases. They learned that the exudative cases presented "the highest incidence of tracheobronchitis, then the mixed cases and then the fibroid." They discovered 36 cases of bronchiectasis in "normal" bronchi and 20 in "tuberculous" bronchi, indicative of a predominance in fibroid as contrasted with caseous disease. They found bronchiectasis to be more frequent in the sputum-negative group, but did not state the site of the disease. Moll (7) concluded that infection alone is able to account for bronchial dilatation without distention from within or traction from without. Numerous authors have noted bronchiectasis to succeed acute pulmonary infections (8, 9, 10).

Atelectasis is known to be frequently followed by bronchiectasis and various authors have commented on the mechanisms involved. A thorough discussion is presented by Lisa and Rosenblatt (11) and need not be repeated here. Crowe (12) has found that in dogs, after bronchial obstruction is produced, bronchiectasis fails to develop unless infection occurs distal to the stricture.

The present study favors the opinion that the development of bronchiectasis may be a result of fibrous pulmonary changes superimposed upon alterations of the bronchi produced by infection. In no case of purely exudative disease was bronchiectasis demonstrated, although clinically, bronchoscopically and/or bronchographically, tuberculous tracheobronchitis was found in all 4 cases. In 9 fibro-exudative cases, 4 instances of bronchial dilatation were found. All of these cases had demonstrated tuberculous tracheobronchitis. In the remaining 30 fibroid cases, 25 had clearly demonstrated bronchiectases.

It is quite possible that the remaining cases also had bronchiectasis, because in some there were bronchial stenoses with lobar atelectases; oil did not enter these divisions. In others, extraneous factors prevented adequate visualization, such as awkwardness of the technicians in the early cases, recalcitrance of some few patients and dismissal of patients before second attempts could be made.

The conclusion suggests itself that, with an increase of pulmonary fibrosis following bronchial infection, the incidence of bronchial dilatation sharply increases.

*Dangers of bronchography:* Bronchographic dangers have been publicized by a few authors and the feeling is prevalent that spread of the disease is a likely consequence.

The injections done in this study were by moderately inexperienced hands. Yet, using lipiodol or iodochloral, very few reactions occurred and no spread was observed with certainty. As many lobes as were desired were injected at a single time.

It is our feeling that this procedure, generally speaking, is relatively innocuous if the patient is premedicated with one and one-half grains of nembutal to help prevent pontocaine reactions.

Use of thorotrast, however, should be discouraged.

*Subsequent radiography:* It cannot be denied that succeeding roentgenograms are frequently obscured by this procedure. Why this occurs in some patients and not in others, we do not know. However, we have observed lipiodol remnants in the parenchyma for as long as three years.

It has been mentioned by many authors, notably by Salkin, Cadden and Edson (1), that bronchoscopy reveals disease principally in major bronchi. It is apparent that contrast bronchography yields far more information about smaller radicles. Bronchiectasis in this investigation was found in as many patients in whom no observer suspected it as in those in whom any of the usual symptoms of bronchial tuberculosis might have led one to expect bronchial disease.

It is remarked in passing by Alexander (13) that bronchial dilatation is responsible for persistent sputum after thoracoplasty. In our small series of thoracoplasties (12 patients) 10 instances of bronchiectasis were found. In 5 of these cases, there was contralateral bronchial dilatation. Eleven of the thoracoplasties were done on patients with fibroid disease. In 8 of 10 cases of fibrotic disease receiving subatmospheric pneumothorax bronchiectasis was demonstrated. In 11 fibroid cases in whom no collapse therapy was done, bronchiectasis was demonstrated 7 times and stenosis 4 times and neither once.

It would appear that the collapse therapy might be of less importance than has been supposed in the production of bronchiectasis. The type of disease underlying the procedure seems to bear far more responsibility. Of course, this series is too small for definite conclusions to be drawn.

It has been the custom throughout the world to suspect bronchiectasis when there was a history of repeated infections of the lungs, sinusitis and copious sputum, sometimes foul. The present study does not bear out the significance of this suggested triad. Here it was found that 13 individuals with proved bronchiectasis, one patient with 4 involved lobes, had less than one drachm of sputum daily, 7 had two drachms to one-half ounce, 7 had one to four ounces and only 3 had more sputum than four ounces. In addition to bronchiectasis, several patients had the irritating factor of bronchial stenosis.

Specifically, disregarding combinations of lobes involved, the following information is derived: right upper lobe bronchiectasis produced less than one drachm of sputum daily in 7 patients, one drachm to one-half ounce twice, one to four ounces twice and more than four ounces once. Left upper lobe bronchial dilatation: no sputum twice, less than one drachm 6 times, one drachm to one-half ounce once, one to four ounces twice and more than four ounces twice. Right middle lobe bronchiectasis was seen only once; this case produced less than one drachm. Left lower lobe bronchiectasis produced less than one drachm thrice, one drachm to one-half ounce thrice, one ounce to four ounces once and more than four ounces twice. Right lower lobe dilatation produced no sputum once, less than one drachm 5 times, one drachm to one-half ounce once and one ounce to four ounces once.

It is recognized that this is a selected group of patients, all of whom have

bronchial and/or pulmonary tuberculosis. Nevertheless, many dependent lobes were involved. There is one source of error which must not be overlooked. There are occasionally dependent bronchiectases in upper lobes. In one case included here this is true. In several of the cases listed as lower lobe disease, the dilatation was not dependent. We are unable to find that this makes any difference in the data given.

The inevitable question arises: Is contrast bronchography worth while as a routine procedure in pulmonary tuberculosis? The answer would seem to be in the negative: (1) It is well known from autopsy findings that fibroid tuberculosis is associated with bronchiectasis. Gross bronchial stenosis almost invariably can be diagnosed otherwise. (2) Contrast media remain in the parenchyma and obscure succeeding roentgenographic changes. (3) Rare reactions occur. Nevertheless, there are definite indications for contrast bronchography. It should be used whenever ordinary roentgenography fails to reveal the source of positive sputum. Thickened pleura, empyema and thoracoplasty often obscure underlying pathological changes. In hospitals where tomography is not available, bronchography is needed in such cases. Where tomography is used, bronchography in these instances is optional.

#### ADDENDUM

Since the present article was written, an extensive study of bronchography in pulmonary tuberculosis has been reported by Dormer, Friedlander and Wiles (14-19). These workers instilled radiopaque substances into the bronchi of some 2,000 tuberculous patients over a period of twenty-five years. They did not give a statistical résumé in the manner of the present report. A perusal of their study is recommended. Their essential conclusions are quoted:

"Let us set down briefly what we have learned from bronchography:

1. That it is safe. We have never seen a case made worse by the installation of lipiodol into the bronchi. It must be noted that no case sensitive to iodides or cocaine is explored in this manner.

2. That block of some portion of the bronchial tree is invariably present in every case of pulmonary tuberculosis unless the area beyond the block has already broken down into a cavity. Even when there is the earliest demonstrable X-ray lesion this block occurs, usually in the bronchioles.

3. As a result of the bronchial or bronchiolar block, there occurs cavitation or bronchiectasis and ultimately a distortion of the bronchial tree due to fibrosis in the affected area.

4. Tuberculous bronchiectasis and cavitation therefore arise in exactly the same way as do nontuberculous bronchiectasis or a pulmonary abscess."

Dormer and his associates came to feel that bronchography was of sufficient clinical importance in pulmonary tuberculosis that they stated: "During the last two years it has become so important that a bronchogram is done in nearly every case in this clinic."

It is the feeling of the present author that they have made a contribution which obviates the necessity for routine bronchography. Their findings are sufficiently clear that under ordinary circumstances one can project the intrapulmonary pathological picture from a knowledge of the type and location of disease present.

## CONCLUSIONS

Fifty unselected tuberculous patients were subjected to contrast bronchography. Bronchiectasis was demonstrated convincingly in 85 per cent of the fibroid, 36 per cent of the fibrocascous and none of the exudative cases. Bronchiectasis was proved unequivocally in many patients in whom it had not been clinically suspected. Collapse therapy apparently bore no relation to the incidence of bronchial dilatation. In tuberculous patients, sputum positivity and quantity were not influenced by the presence or absence of bronchiectasis, with or without stenosis; while bronchial stenosis presented positive sputum in each of the 13 cases in which it was demonstrated, it had no relation to its quantity.

## CONCLUSIONES

Empleada la broncografía de contraste en 50 tuberculosos tomados al azar, se demostró en forma convincente la presencia de bronquiectasia en 85% de los fibrosos, 36% de los fibrocascosos y en ninguno de los casos exudativos, comprobándose claramente su existencia en enfermos en quienes no se había sospechado clínicamente. La colapsoterapia al parecer no guardó relación alguna con la incidencia de la dilatación bronquial. En los tuberculosos la positividad y la cantidad del esputo no fueron afectadas por la presencia o ausencia de bronquiectasia con o sin estenosis; mientras que la estenosis bronquial dió esputo positivo en cada uno de los 13 casos en los que existió sin guardar relación con la cantidad del mismo.

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# OLEOTHORAX<sup>1</sup>

A Reëvaluation—With a Final Report of 101 Cases

R. H. BROWNING, E. S. RAY<sup>2</sup> AND LOUIS ROTENBERG

In 1941 (1), two of the above writers (Browning and Ray) collaborated in a report of 101 cases of oleothorax used in the treatment of tuberculosis between December, 1931 and July, 1939. In 48 of these cases the indication for oleothorax was persistent tuberculous empyema, while in 53 cases the indication was obliterative pleurisy. At that time the minimum period of observation was six months. Most cases, however, had been followed for twelve months or longer. Seventy-five of the 101 cases were successful at the time of that study. Of the 26 unsuccessful cases 6 had bronchopleural fistula, 3 had pleurocutaneous fistula and 17 had persistent or recurrent empyema. In that report our results in the cases selected were thought to be very satisfactory considering the original status of the lungs.

A recent survey (2) of collapse therapy in this country shows that oleothorax is being used with significant frequency. This may be due in part to the influence of our original paper. During the six-year period since the original report, there have been a number of developments which have altered our use of oleothorax and our attitude toward it. Because our present conclusions concerning oleothorax therapy are radically different from those in our previous report, we feel a definite responsibility in reëvaluating our results and stating our present views on the subject.

We have attempted to make a follow-up study of the 75 cases of oleothorax that were classed as successful in 1941. This has been possible in 70 cases (93 per cent).

In 13 of these cases oleothorax has been continued (table 1). In none of these have there been any complications due to oleothorax. The 8 cases, living and well, have been advised to discontinue their oleothorax but have refused because they feel well and are reluctant to make any change in their treatment. It is likely that some of these have unexpandable lungs.

The cases of oleothorax originally successful that have developed complications are shown in table 2. There are 14 cases (20 per cent of the 70 cases) in this group. Eight of the 14 developed bronchopleural fistula with death resulting in 5 cases. Six of the 14 suffered a recurrence of empyema and because of this the oil was removed.

The largest group contains those cases with satisfactory oleothorax that were voluntarily converted to pneumothorax with reëxpansion<sup>3</sup> of the lung being at-

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<sup>3</sup> The terms "expandable" and "reëxpansion" are used in this paper as a matter of convenience. Reëxpansion really means that no air, oil or exudate is demonstrable any more

tempted. There are 43 cases in this group. Their present status is shown in table 3. The reason for conversion in many patients was the fear of late complications which were being encountered in the oleothorax group as a whole. However, in a number of these cases reëxpansion was attempted because the period of collapse was considered to be adequate. Thirty-three patients are living and well, although in only 12 of these has "complete reëxpansion" of the lung occurred. Of the 43 cases in this group there has been "complete reëxpansion" of the

TABLE 1

*13 cases of uncomplicated oleothorax that were continued*

Working . . . . .	8
Ill (not due to oleothorax) . . . . .	2
Dead (not related to oleothorax) . . . . .	3

TABLE 2

*14 cases of oleothorax with complications*

	BRONCHOPLEURAL FISTULA	RECURRENT EMPYEMA
Working . . . . .	1	6
Ill (not due to oleothorax) . . . . .	2	0
Dead (directly due to oleothorax) . . . . .	5	0

TABLE 3

*43 uncomplicated cases of oleothorax voluntarily converted*

	LUNGS EXPANDED	LUNGS* PROBABLY EXPAND- ABLE	LUNGS UNEXPAND- ABLE	LUNGS UNEXPAND- ABLE WITH EMPYEMA	†EXPANSION UNDETER- MINED
Working . . . . .	12	5	13	3	0
Ill (not due to oleothorax) . . . . .	3	1	1	0	0
Dead (not due to oleothorax) . . . . .	1	0	0	1	3

\* Probably expandable refers to cases in which pleural space has capacity of less than 300 cc.

† Death resulted soon after removal of oil—death due to tuberculosis in two cases and to lobar pneumonia in one case.

lung in 37 per cent of cases; reëxpansion is "probable" in 14 per cent; and the lungs are unexpandable in 42 per cent. The term "probably expandable" is applied where there is a pleural space remaining that holds not more than 300 cc. of air or fluid.

A study was made also of all patients, of the original series of 101, in whom

between visceral and parietal pleurae. The authors recognize that in most patients treated with oleothorax the visceral pleura of the treated lung is markedly thickened and that in many cases the underlying lung is also fibrotic. "Reëxpansion" when it occurs must result from varying degrees of shift of the mediastinum, elevation of the diaphragm, contraction of the chest wall and actual expansion of the lung.

reexpansion was attempted and in whom the reexpansion period was sufficient to determine the expandability of the lung (table 4). There were 46 cases that could be so studied. Included in this group were cases in which complications occurred as well as cases where reexpansion was voluntarily attempted. The relationship of duration of oleothorax to the expandability of the lung was also examined. The great majority of the patients in whom the lung could be expanded were those with a duration of oleothorax of less than four years, while obliteration of the pleural space was not achieved in any case where the duration of oleothorax was six years or longer. Out of 46 patients the lungs were "completely expanded" in 19 (41 per cent), "probably expandable" in 6 (13 per cent) and unexpandable in 21 (46 per cent). Of course, some of the unexpandable

TABLE 4  
*Expandability of lungs following oleothorax*

DURATION OF OLEOTHORAX	EMPYEMA			OBLITERATIVE PLEURISY			TOTAL
	Expanded	Probably expandable	Unexpandable	Expanded	Probably expandable	Unexpandable	
1-2 years.....	2			2			4
2-3 years.....	2		1	4		2	9
3-4 years.....	2			2	1	3	8
4-5 years.....		2	3	2	1	3	11
5-6 years.....	1			2	1	1	5
6-7 years.....		1	2				3
7-8 years.....							
8-9 years.....						2	2
9-10 years.....			1				1
10-11 years.....			3				3
Total.....	7	3	10	12	3	11	46

lungs are the seat of extensive fibrotic disease and it is impossible to determine the number failing to expand solely because of thickening of the visceral pleura.

While many of these patients with unexpandable lungs are living and working, they cannot be considered well, and their prognosis is certainly impaired by a persistent pleural space. Thoracoplasty would be necessary to obliterate these pleural spaces.

Observation of this group over a period of time has demonstrated several important findings:

(1) There is a cumulative incidence of late complications in long continued oleothorax (table 2). The most serious is bronchopleural fistula which, as a late complication, probably results chiefly from asymptomatic formation of pleural exudate beneath the oil with development of positive intrapleural pressures.

(2) Safe medical observation of these oleothorax patients was difficult following their discharge from the hospital. Because of prolonged periods without symptoms or signs, both patients and their physicians tend to be lulled into a false sense of security. Exploratory aspirations are deferred too long, mild symp-

toms are not reported, and in some instances considerable quantities of fluid may be permitted to accumulate with disastrous results.

(3) Conversion of oleothorax to pneumothorax was followed almost universally by a recurrence of fluid which was in most cases purulent or seropurulent. It has been our practice, when reëxpansion is desired, to permit the pleural spaces to fill with fluid and not to add more air. Closed aspiration is performed periodically to the point of discomfort. Under such a regimen the fluid changes gradually until it has attained a serous character. These patients seem to follow a uniformly benign course without complications. This procedure has worked out equally well whether or not the lung was expandable.

As a result of these findings we now recommend the following procedure: Once the purpose of oleothorax has been accomplished (perhaps after eighteen to twenty-four months), the oil should be aspirated and replaced with air. Decision to attempt reëxpansion is then determined by the extent and status of the pulmonary lesion. The patients continuing under oleothorax therapy should have at least semimonthly fluoroscopy and diagnostic needling at the base of the pocket.

In the discussion above we have attempted to give some of the conclusions resulting from a late follow-up of oleothorax cases. Still more significant than these in determining the use of oleothorax have been other changes in collapse therapy policy at this hospital.

#### OLEOTHORAX AS RELATED TO OTHER FORMS OF COLLAPSE THERAPY

As originally stated in our series, oleothorax had two indications: (1) inhibition, (2) disinfection.

*Inhibition:* With improvement in the results of surgical treatment of tuberculosis, we no longer feel so much concern over the collapsed lung which is expanding involuntarily. Such a lung, if pleural fluid is not present, can usually be maintained in a fair state of collapse with positive intrapleural air pressures. We believe that in any patient, having an appreciable quantity of persistent fluid, the lung should be reëxpanded with dependence being placed on other collapse therapy measures if needed. We therefore no longer use oleothorax to prevent reëxpansion of a collapsed lung.

*Disinfection:* The problem of persistent tuberculous empyema without secondary infection is still a difficult one. Our present opinion is similar to that expressed in the previous report. This was to the effect that thoracoplasty is the procedure of choice, but that, in those patients who are not reasonable surgical risks, oleothorax should be considered. Despite this remaining indication for oleothorax, our use of this procedure for disinfection purposes has dropped practically to zero. This change results from the fact that our incidence of tuberculous empyema has been greatly reduced.

With the thought that some others who are plagued by a high incidence of acute effusions and tuberculous empyema during the course of pneumothorax therapy might be interested, we are listing below the factors which seem to be responsible for the reduction in our empyema incidence:

(1) Prompt abandonment of pneumothorax when a satisfactory and effective collapse cannot be obtained. (Pneumonolysis should be attempted when possible, of course.)

(2) Early abandonment of pneumothorax and attempts at reëxpansion in the presence of acute effusions, and even in the presence of asymptomatic effusions if fluid persists for more than a few weeks and the rate of formation is not diminishing.

(3) The most important factor in the reduction of empyema cases is the result of the present management of acute, exudative lesions. Pneumothorax is no longer induced during the acute, febrile period. Instead, these patients are placed on bed-rest for several months. Temporary phrenic paralysis and pneumoperitoneum are used as adjuncts in most cases. The use of these combined procedures has been most impressive as regards the extent of collapse obtained, the effective control of existing disease and freedom from complications. After the tuberculous process has become less acute, as manifested by a return of the temperature to normal and the disappearance of other constitutional symptoms, pneumothorax is frequently induced. There has been a gratifying decrease of pleural complications in these acute lesions and, in addition, there has not been any appreciable increase in the number of pleural adhesions resulting from this policy of delayed pneumothorax.

#### CONCLUSIONS

To-day, we believe that oleothorax has a very limited place in the treatment of tuberculous empyema. Early reëxpansion of the lung with obliteration of the pleural space is certainly the most effective method of treating empyema. Where reëxpansion proves to be impossible, closure of the space by thoracoplasty is usually indicated. However, in cases where reëxpansion is impossible and where the general condition of the patient is too poor to stand a major surgical procedure, one is probably justified in converting the pneumothorax to oleothorax. Such patients should be under close observation with careful fluoroscopy and diagnostic needling of the pleural space at one to two-week intervals.

In cases of obliterative pleurisy, one is not justified in converting the pneumothorax to oleothorax. If the pneumothorax space cannot be maintained by positive pressures, the lung should be reëxpanded and other collapse therapy measures considered.

#### SUMMARY

Report is made of follow-up study of 70 cases of oleothorax that were uncomplicated at the time of our 1941 report:

Bronchopleural fistula developed in 8 cases (11 per cent).

Empyema recurred in 6 cases (9 per cent).

In 46 cases (including complicated as well as uncomplicated cases) where adequate attempt at reëxpansion of the lung was carried out, there were 21 cases (46 per cent) with unexpandable lungs.

As a result of these findings and the diminishing incidence of tuberculous empyema in our collapse therapy program, our use of oleothorax has become very infrequent.

#### SUMARIO

Versa este estudio sobre la observación subsiguiente de 70 casos de oleotórax que no mostraban complicaciones al informarse sobre ellos en 1941:

En 8 (11 por ciento) se presentó fístula broncopleurál.

En 6 (9 por ciento) recurrió el empiema.

Entre 46 (comprendiendo casos con y sin complicaciones) en los que se hicieron esfuerzos adecuados para expandir de nuevo el pulmón, hubo 21 (46 por ciento) en que fracasó la tentativa.

Por virtud de estos hallazgos y de la decreciente incidencia del empiema tuberculoso en nuestras obras de colapsoterapia, el empleo del oleotórax se ha vuelto muy raro en nuestro servicio.

#### *Acknowledgment*

Thanks are due to Miss Mary Dancho for assistance in obtaining follow-up information.

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## DIETARIES IN TUBERCULOSIS SANATORIA

Report of the Approximate Nutritional Evaluation of Thirty-four County  
Tuberculosis Hospital Diets during 1943 and 1944

JANE SEDGWICK<sup>1</sup>

Dietaries of 34 tuberculosis hospitals throughout the State of California were studied during 1943 and 1944 by nutritionists on the staff of the California State Department of Public Health.<sup>2</sup> The survey in each institution had as its aim a determination of the nutritional adequacy by means of a method employing nutritional accounting.<sup>3</sup> One day's food, including standard nourishments, was weighed or measured. A sample meal from the general patients' menu was drawn during food service. Calculations were made to determine the specific nutrients supplied. In some instances two days' food was studied and in one hospital the average pounds of food in the 15 large food groups per person per day were determined from the usage for a month. One day's menu is only an approximate indication of the adequacy of the diet. Greater accuracy can be obtained in the determination of the adequacy of the food offered if the amount of food used for a period of four weeks is studied.

A standard for the recommended allowance of specific nutrients for tuberculosis patients was selected by Dr. Kupka, Chief of the Bureau of Tuberculosis of the California State Department of Public Health. This standard was based on the Recommended Daily Allowances for Specific Food Nutrients furnished as a yardstick by the Food and Nutrition Board of the National Research Council for the sedentary man. Dr. Kupka increased the protein and ascorbic acid allowance above the recommended needs of the sedentary man after consultation with tuberculosis specialists at the Medical Schools of Stanford University and the University of California. The results of the calculations of the day's dietary served were compared with the following standard:

### *Recommended Daily Allowances for Specific Food Nutrients for Tuberculosis Patients*

Calories.....	2,500
Protein.....	85 to 125 g.
Calcium.....	0.8 g.
Iron.....	12.0 mg.
Vitamin A.....	5,000 International Units
Thiamine.....	1.5 mg.
Riboflavin.....	2.2 mg.
Niacin.....	15.0 mg.
Ascorbic acid.....	100 to 125 mg.

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<sup>2</sup> Reports of Dietary Studies of Sanatoria are on file in the Bureau of Tuberculosis of the California State Department of Public Health.

<sup>3</sup> JANE SEDGWICK: The Berryman-Howe short method of calculating the nutritive value of diets in large scale feeding, Bull. California Dietetics A., Spring issue, 1945, Vol. XII, No. 1.

The above specific nutrients can easily be supplied by the following quantities of natural food per person per day by selecting amounts from the large food groups. Common foods may be arranged by classes or groups on the basis of similar nutritive content or of unique contribution to the diet.

<i>Food Group</i>	<i>Pounds per Person per Day</i>
Meat, fish and poultry (carcass weight).....	0.70
Eggs.....	0.125 (1 egg)
Milk and milk products.....	2.16 (34½ fluid oz.)
Butter.....	0.045
Other fats.....	0.03
Grain products.....	0.20
Legumes, dry.....	0.02
Sugars and syrups.....	0.12
Vegetables, yellow, green, leafy.....	0.40
Tomatoes.....	0.157
Citrus.....	0.75
Potatoes.....	0.33
Other vegetables not included above.....	0.33
Fruits other than citrus.....	0.14
Dried fruit.....	0.01

Dietary reports were obtained on 30 of the 34 hospitals studied. Twenty-two of these hospitals employed dietitians. A study of the dietary evaluations as compared with the standard revealed the following information:

*Calories:* Sixteen, or more than one-half, of the hospitals were found to be below the recommended allowance for the daily caloric intake. Eight were within a range of  $\pm 10$  per cent of the recommended level of intake. Five were more than 10 per cent above the recommendation. The lowest calorie intake measured 1,605 and the highest 3,695 calories.

*Protein:* Ten hospitals fell below the lower limit recommended for protein. Two were 18 per cent and 20 per cent below the lower limit. Twenty fell within the recommended range.

*Calcium:* No hospitals fell below the recommendation, 8 were adequate and 7 had more than 10 per cent above the requirement. One hospital had 180 per cent of the recommendation.

*Vitamin A:* Only one hospital fell below the recommended standard, 22 were within 10 per cent above the recommended amount and 7 were more than 10 per cent above, some as much as 300 per cent.

*Thiamine:* This specific nutrient was low in 18 of the 30 hospitals. Four were within 10 per cent of the requirement and 8 were above 10 per cent more than the requirement.

*Riboflavin:* None of the hospitals showed a shortage of this vitamin. This would not be unexpected because of the high intake of milk, which also furnished the high calcium content of the diets. Thirteen hospitals were within the range of 10 per cent above the recommendation. Seventeen were very much above—a few as high as 70 per cent above the requirement.



*Niacin:* Only 6 of the dietaries were studied for niacin and all were below the recommendation.

*Ascorbic acid:* Although this food nutrient has been stressed in the treatment of tuberculosis, 17 of the 30 hospitals studied were low in this respect, some of them as low as 70 per cent below the recommendation. Six fell within a range of 10 per cent above and 5 were more than 10 per cent above the recommended allowance.

The outstanding deficiencies were shortages of calories, protein, thiamine and ascorbic acid. Niacin was studied in only a few of the hospital dietaries but it is significant that all those that were studied were low. Inadequate protein would go hand in hand with a shortage of thiamine and niacin as it is in those foods which are protein-rich that the largest supply of these vitamins is found.

The conclusions which may be drawn as a result of this study may be stated as follows:

(1) Hospitals are convinced of the importance of serving milk. This results in adequate calcium and riboflavin.

(2) Inadequate calories, protein, thiamine and ascorbic acid in from 30 per cent to more than 50 per cent of the hospital dietaries studied indicates that considerable change needs to be made in the quantity and kind of food served in these hospitals. The employment of a dietitian does not seem to insure the adequacy of the diet served.

There is a need for a rapid and fairly accurate method of determining the approximate nutritive value of diets served in a hospital over a period of time. Nutritional accounting may be used as a measure of adequacy of the diet in conjunction with cost accounting. It is recommended that hospitals which serve patients for a period longer than ten days establish some method of calculating the nutritive value of the food used in relation to the number of persons served. A ration per man per day can be established which can be used as a yardstick for measuring the adequacy of the diet and can also be used to order and issue supplies for use over a period of a day, week or month.

#### PREPARATION OF FOOD

It is possible to have an adequate daily menu in relation to the specific nutrients, but this menu may become inadequate through poor food preparation.

Food preparation includes all processes through which food passes up to the time it is served. It includes the use of formulas to prepare uniform dishes on the menu; care in preparation to conserve nutritive value of the food—this is particularly true of the heat-labile B vitamins (thiamine and niacin) which are destroyed by prolonged cooking at high temperatures, and of the water-soluble vitamins B and C of which the loss in cooking water may be extensive; avoidance of excessive trimming losses in preparation; prevention of pilfering, theft and handouts; maintenance of eye appeal by use of individual portions, garnishes, toast and other devices; having all menu items ready on time but not too far ahead of time, and making all food as nearly comparable as possible to accepted standards which

insure palatability by the development of a pleasant taste and an appetizing flavor. The methods of food preparation were judged on the basis of the above items and, in the 30 hospitals studied, methods of food preparation were judged decidedly poor in 4 (2 of these employed dietitians), fair in 9, and good in 17. Lack of authority or lack of adequate nutritional information is the cause of poor food preparation where dietitians are employed. It might be desirable to make available to these hospitals a consulting dietitian who can improve methods of food preparation and encourage more adequate diets.

#### MENU PLANNING

Variety, color and flavor are extremely important in menus for the tuberculosis patient. He remains in the hospital months on end and the food can become very monotonous if it is not carefully planned. Only one day's menu was listed in the dietary reports of the hospitals; however, comments such as these are found in the reports:

"There is lack of imagination in the planning of meals. The same combinations are repeated again and again. A check of a year of the menus will show that the supper meals are particularly monotonous—meals are repeated and flavors repeated in the same meal."

"Menus were checked for thirteen consecutive weeks . . . A record of the main dishes served at dinner and supper indicated that there was no great repetition of food served or of food combinations."

In all but 2 or 3 places, more whole grain cereals should be used. Also, there is a need for more high vitamin C juices, fruits and vegetables. These should be substituted for some of the milk beverages used between meals. Too much milk is found in many menus. This takes away the appetite of the patient for more solid foods. More than a quart a day was served to the patients in the majority of hospitals. This should be cut to a maximum of one quart per person per day including the milk used in cooking.

In addition to the topics already discussed the reports contained comments on special diets, nourishments, food purchasing, kitchen equipment, meal hours, food service and the use of vitamin concentrates.

#### SUMMARY

A standard for the specific food nutrients recommended for the tuberculosis patient is presented. A summary of the approximate nutritional evaluation of the menu served in 30 subsidized California County Tuberculosis Hospitals during 1943 and 1944 is presented. It is evident that 50 per cent of the hospitals were deficient in protein, thiamine and ascorbic acid and 30 per cent were deficient in calories, for the days on which the studies were made.

Since food and nutrition are considered one of the important therapeutic aids in this disease, steps should be taken to improve food service to correct these nutritional inadequacies. The employment of a consulting dietitian or nutritionist by the State may aid the County Tuberculosis Hospitals in bringing

about needed changes. Sample studies of diets served in hospitals can be made and assurance can be given to superintendents of institutions that the diet is nutritionally adequate.

#### SUMARIO

Preséntase un patrón para las sustancias nutritivas específicas recomendadas para el tuberculoso. Ofrécese también un sumario de la evaluación nutritiva aproximada de las comidas servidas en 30 Hospitales para Tuberculosos de California, durante 1943 y 1944. Salta a la vista que el 90% de los hospitales suministraban dietas deficientes en proteína, tiamina y ácido ascórbico, y 30% en calorías, durante los días en que se hizo el estudio.

Toda vez que los alimentos y la nutrición están considerados entre los auxiliares terapéuticos más importantes en esta enfermedad, deben tomarse medidas para el mejoramiento de las dietas a fin de corregir esas deficiencias nutritivas. El empleo de una dietetista o nutricionista por el Estado puede ayudar a realizar los cambios necesarios. Se pueden llevar a cabo estudios representativos de las dietas servidas en los hospitales asegurando así a los directores de estas instituciones que la alimentación es adecuada desde el punto de vista nutritivo.

# TUBERCULOUS PLEURISY WITH EFFUSION<sup>1</sup>

## A Manifestation of Extrapulmonary Tuberculosis

EDWARD G. JONES<sup>2</sup> AND MYRTLE DOOLEY<sup>3</sup>

The prognosis of the patient with tuberculous pleurisy with effusion is usually assumed to be more favorable than for patients with pulmonary tuberculosis. This attitude is based on reliable studies of patients (adult Caucasians) who have been followed carefully for a number of years after the effusion first developed (1). If, however, it is shown that pleurisy with effusion is a manifestation of widespread extrapulmonary tuberculosis, then prolonged complete bed-rest is imperative, and obviously any neglect of this phase of treatment is dangerous. Tuberculosis in the Negro living in Africa has been shown to be frequently of this form (2). The following study will demonstrate that, among the Negro population of Baltimore, tuberculous pleurisy with effusion often is a manifestation of one of the most serious forms of tuberculosis. This occasionally may also be true in white patients.

### CLINICAL AND LABORATORY METHODS

In the Baltimore City Hospital, during the past fifteen years, patients with pleurisy with effusion have been treated by strict bed-rest during the time when acute symptoms were present, and have been maintained on this regimen until fluid stops forming and the blood sedimentation rate falls to within normal limits. Chest fluid has been removed in order to diagnose by roentgenogram any parenchymal lesion which would otherwise be obscured by fluid, or in order to relieve dyspnea. The fluid in every case has been cultured for tubercle bacilli, but the fluid often has proved sterile. The patients have been discharged only after the sedimentation rate has remained within normal limits for from one to three months and acute symptoms have subsided. All roentgenograms have been read by a trained roentgenologist as well as by a senior member of the consulting staff. Sputum examinations have included, in every case, seventy-two-hour concentrated specimens, sputum cultures and repeated examinations of gastric washings. The examinations of sputum, other laboratory data, and roentgenographic interpretations have been recorded carefully throughout the years covered by this survey. Therefore, we can state with considerable certainty that none of the patients in this series had a positive sputum, nor were there any parenchymal lesions diagnosed. The patients who later developed pulmonary tuberculosis deserved a special review of the chest findings during their initial hospitalization. Therefore, roentgenographic interpretations were rechecked by one of us (E. J.) and any patient whose films had shown a "suspicious" or "questionable" paren-

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chymal lesion was excluded from the series now reported. Each patient after leaving the hospital was periodically visited by a public health nurse, and her reports were forwarded to the Bureau of Tuberculosis for the City of Baltimore. This Bureau has kept an accurate record of patients admitted to the City Hospital and all State Sanatoria, and with the Department of Vital Statistics has maintained a record of all deaths caused by tuberculosis occurring in Maryland. Therefore, the statistics we have utilized show all recurrences or associated tuberculous lesions among tuberculosis patients within the State requiring hospitalization and all deaths from tuberculosis in Maryland.

#### TYPE OF PATIENT, TREATMENT AND RESULTS

There were 144 patients discharged from the hospital (either alive or dead) with a diagnosis of tuberculous pleurisy with effusion and without pulmonary parenchymal lesion. This group was composed of 69 Negro men, 37 Negro

TABLE I  
*Age distribution of patients with tuberculous pleuritis with effusion and without other tuberculous lesions*

AGE	NEGRO		WHITE		TOTAL
	Male	Female	Male	Female	
13-19	22	13	2	4	41
20-29	25	17	10	12	64
30-39	14	6	4	1	25
40-49	3	0	3	0	6
Over 50	5	1	2	0	8
Total					144

women, 21 white men and 17 white women. The age of the youngest patient was 13 and that of the oldest 62. The age distribution is recorded in table 1, and the age distribution of those with associated tuberculous lesions elsewhere in table 2. It will be seen that, either on admission or sometime during the course of studies, 37 patients showed tuberculosis other than unilateral pleurisy with effusion, although, as mentioned above, none of the lesions involved the lung parenchyma during the patient's first hospitalization. During the initial hospitalization extrapulmonary forms of tuberculosis were diagnosed in 20 patients and 6 others developed extrapulmonary evidence of tuberculosis later. Twenty-three of these 26 patients were Negro; 16 of the 26 are known to have died of tuberculosis; 5 are well and have remained in good health for more than one year; 5 were not followed for as long as one year. The extrapulmonary forms of tuberculosis in those that remained well were peritonitis, 3; osteitis, 1; adenitis, 1. Seven of the 16 died during the first admission, 9 on subsequent admissions. The associated lesions are listed in table 3.

An attempt was made to follow all patients at frequent intervals for twelve to

eighteen months after hospital discharge. After this length of time many patients were discharged as completely arrested. However, later reports were sometimes noted. For example, a notation of good health was made after thirteen years for one patient, and the last report of good health on all patients remaining well averaged three years.

TABLE 2

*Age distribution of patients with tuberculous pleuritis with effusion and with associated tuberculous lesions elsewhere*

AGE	NEGRO		WHITE		TOTAL
	Male	Female	Male	Female	
<i>years</i>					
13-19	5	7	0	0	12
20-29	10	5	0	2	17
30-39	4	0	1	0	5
40-49	1	0	0	0	1
Over 50	1	0	1	0	2
Total.....					37

TABLE 3

*Types of extrapulmonary tuberculous lesions associated with pleuritis with effusion*

	NEGRO		WHITE		TOTAL
	Male	Female	Male	Female	
Bone.....	3	0	1*	0	4
Polyserositis.....	2	1	0	0	3
Peritonitis.....	5	4	0	0	9
Meningeal.....	2	2	0	0	4
Adenitis.....	2	2	1	0	5
Renal.....	0	0	2	0	2
Miliary.....	2	1	0	0	3
Total in 26 patients.....					30

\* Same patient had renal disease.

Forty-two of the patients could not be followed for one year after discharge from the hospital and 3 others are known to be well but as yet have not been out of the hospital for a full year. This leaves a total of 99 patients who have been followed for more than one year or have died of tuberculosis. Of these, 64 have been followed carefully for at least one year and there has been no report of active tuberculosis. Thirteen patients died with pulmonary tuberculosis, but 10 of these also had extrapulmonary tuberculosis. Three others developed pulmonary tuberculosis which has not proved fatal.

In the series covered there were 9 instances of bilateral pleurisy with effusion. Six of these patients on the first admission showed no extrapulmonary lesion, but

one had enlarged hilar lymph nodes, one had ascites and one developed bilateral effusion after having had unilateral effusion on admittance. Three of these 9 patients could not be followed as long as one year, and 5 other patients died from other forms of tuberculosis, namely: bone and renal, polyserositis, peritonitis, miliary, and pulmonary.

Four patients showed only unilateral pleural effusion during the first hospitalization, but later developed extrapulmonary manifestations of tuberculosis. Also,

TABLE 4  
*Duration of initial hospitalization*

MONTHS	PATIENTS WITH UNILATERAL EFFUSION	PATIENTS WITH BILATERAL EFFUSION	PATIENTS WITH EFFUSION AND EXTRAPULMONARY TUBERCULOSIS
3	22	0	0
6	19	1	2
9	11	1	4
12	5	1	3
24	2	0	0
48	1	1	0
Total.....	60	4	9

TABLE 5  
*Months until reactivation of tuberculosis in patients discharged as arrested*

	NUMBER OF REACTIVATIONS
3 months.....	4
6 months.....	1
9 months.....	1
12 months.....	3
24 months.....	4
96 months.....	1
15 years.....	1
	15

15 instances of reactivation in 10 patients.

one white and one Negro patient, both with bilateral effusion on first hospitalization, later developed additional evidence of purely extrapulmonary tuberculosis. Two colored patients who had unilateral effusion and enlarged hilar nodes on the first hospitalization later developed meningeal and miliary tuberculosis.

Of the patients discharged from the hospital as arrested, 61 remained well. (It was previously stated that 64 of the patients remained well for over one year, hence 3 of the patients who left the hospital against advice had no further complications necessitating hospitalization.) Ten patients showed a reactivation of tuberculosis and 4 of these were patients who left the hospital within three months' time. Eight of the 10 patients with complications who were able to

leave the hospital as arrested, and who followed the treatment recommended, remained well. However, the earliest any of these left the hospital was five months and the longest stay was four years. This latter patient had bilateral pleural effusion and on a subsequent admission had recurrence of the effusion, but this time he was able to leave the hospital in six months; he is the only patient with bilateral effusion who is known to have remained well for more than one year.

Table 4 tabulates the length of stay in the hospital of those patients discharged as arrested and table 5 shows how soon after discharge reactivation of tuberculosis occurred among these patients; however, there was no record of follow-up of some of the patients until their death from tuberculosis was reported.

#### DISCUSSION

This report reveals that pleurisy with effusion often is a manifestation of wide-spread extrapulmonary tuberculosis in the Negro of this locality and there are 4 instances of similar developments among white patients. It is clear that this response to the tubercle bacilli by the Negro in North America is similar to that which has been described in the African Negro (2). Furthermore, besides the statistical evidence presented that this is a racial characteristic, culture and typing of organisms from a Negro patient with unusual extrapulmonary forms of tuberculosis have shown that the tubercle bacillus studied did not represent any unusual type of organism, but on the contrary, the bacilli were a virulent human strain (by culture study and animal inoculation in guinea pig, rabbit and chicken) common in white patients with pulmonary tuberculosis (3). Only rarely does the Caucasian patient develop an extensive extrapulmonary form of tuberculosis. However, a bilateral pleural effusion, either in a Negro or Caucasian, generally means that there is also wide-spread tuberculosis elsewhere and, in our series, the outcome has been fatal in a majority of these. When, in addition, there is enlargement of the hilar nodes or adenitis elsewhere the lymphogenous type of tuberculosis is established with certainty. Borrel noted that a supraclavicular node often was palpable and was an indication of this form of tuberculosis when there was no other evidence of the disease (2). In a search for adenitis or evidence of scrostitis, a roentgenogram of the abdomen often is indicated.

Any attempt to improve prognosis in tuberculosis should emphasize first the early diagnosis and hospitalization of patients, for unnecessary delay is still common. Furthermore, the present series demonstrates the importance of certain diagnostic procedures and the advisability of new standards in regard to the length of time which the patient should be supervised. Reactivation of tuberculosis in the group studied occurred usually within two years and chiefly among those discharged after a period of hospitalization of only two to three months. This indicates that the preferable treatment of pleurisy with effusion should allow the patient as much bed-rest as one with any other form of acute tuberculosis, and the follow-up period of these patients should extend over at least a two-year interval. Probably several patients in the present series who developed a pulmonary lesion would have had a demonstrable parenchymal lesion diagnosed



on first admittance if the patient had not left the hospital against advice before an adequate chest film could be made. The diagnosis of the chest condition necessitates removal of the pleural fluid, so that an adequate roentgenogram can be made. Certainly a stereoscopic and lateral film of the chest should be made when a parenchymal lesion is not obvious otherwise.

It is to be hoped that early diagnosis, hospitalization and the routine advised above may produce a more favorable prognosis for the patient with pleural effusion and wide-spread extrapulmonary tuberculosis, whereas during the period of this study pleural effusion was often concomitant with a highly fatal form of the disease.

## SUMMARY

1. A study has been made of pleurisy with effusion among colored and white patients of the same community.
2. This study showed that effusion is often the only intrathoracic manifestation of wide-spread extrapulmonary tuberculosis in the Negro; occasionally this is also true in the Caucasian patient.
3. The prognosis of Negro patients with pleurisy with effusion should be guarded, for in this study about one out of 6 of the patients died of tuberculosis which was principally of extrapulmonary form. Furthermore, bilateral pleurisy with effusion is almost always a manifestation of wide-spread extrapulmonary tuberculosis and the outcome has been fatal in most of our patients.
4. We believe that treatment for pleural effusion should be as prolonged as for acute rapidly changing pulmonary tuberculosis, and the patient should be on strict bed-rest for several months after all clinical and laboratory signs are normal. There should be a careful plan of follow-up of these patients for at least two years after discharge from the hospital. An accurate diagnosis cannot be made without removing all pleural fluid and taking a stereoscopic and lateral roentgenogram of the chest to rule out a parenchymal lesion.

## SUMARIO

1. Un estudio de la pleuresía con derrame fué llevado a cabo entre enfermos blancos y en negros de la misma colectividad.
2. Este estudio demostró que el derrame es frecuentemente la única manifestación intratorácica de la tuberculosis extrapulmonar difusa en el negro; ocasionalmente esto reza también con el enfermo caucásico.
3. En los negros con pleuresía con derrame el pronóstico debe ser reservado, pues en este estudio aproximadamente uno de cada seis enfermos murió de tuberculosis que fué principalmente extrapulmonar. Además, la pleuresía bilateral con derrame es casi siempre una manifestación de tuberculosis extrapulmonar diseminada y el resultado ha sido fatal en la mayoría de estos enfermos.
4. El tratamiento del derrame pleural debería ser tan prolongado como el de la tuberculosis pulmonar aguda que varía rápidamente, y el enfermo debe guardar reposo absoluto en cama durante varios meses después de normalizarse todos los síntomas clínicos y de laboratorio. Debería existir un plan de observación

subsecuente de esos enfermos, por lo menos durante dos años después de haber sido dados de alta del hospital. No puede hacerse un diagnóstico exacto sin eliminar antes todo el líquido pleural y tomar un roentgenograma estereoscópico y lateral del tórax para excluir la presencia de una lesión parenquimatososa.

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# TUBERCULOSIS AS AN OCCUPATIONAL HAZARD DURING MEDICAL TRAINING<sup>1</sup>

Report of a Case-finding and Follow-up Study, with an Effective Control Program for Tuberculosis in Women Medical Students

SARAH I. MORRIS

Tuberculosis control in students of medicine represents one of our grave modern medical problems.

It is quite obvious that a potential hazard exists when, "in line of duty," young medical students are intimately exposed, at their most vulnerable age, to tuberculous patients and materials, a risk essential to their training and beyond their own power to control (16).

Numerous investigations (8, 17, 29) have definitely demonstrated, by the tuberculin test, that rapid infection with tuberculosis takes place while in medical school and that, in a lamentable number of cases, active tuberculous disease follows, either while in college or soon thereafter (6, 22, 31).

Investigators in this field have, for some time, recognized this hazard in medical schools and hospitals (17, 22, 31) but the extent and gravity of the problem have not been fully realized by some of our medical educators and hospital officials whose specific duty it should be to safeguard the young vulnerable adults entrusted to their supervision during their training period. Medical students, interns and residents, while rendering valuable service to the medical profession and the public, are facing hazards not generally recognized (8, 22).

The short time available for observation of medical students while resident in college and the insidious onset and chronic course of tuberculosis make necessary an extension of observation beyond medical school into internship and residency to evaluate properly the hazard of exposure in medical school. In the male, the number of active cases developing during medical school years may not attract the attention of the medical school authorities, as the peak of morbidity and mortality for men falls beyond the average age of students. Were routine entrance and periodic X-ray examinations made obligatory for internships and residencies (27, 31), more complete and accurate evidence would be available.

In most sanatoria an unusual number of students and graduates of medicine and nursing will be found to have been patients or, with arrested disease, are on the staffs of such institutions.

Hazards must necessarily be the same in all schools with comparable curricula unless a control program is in operation. The divergent and misleading reports from different schools reveal merely varying interest and efforts to recognize infected and diseased students, a lack of uniformity in criteria or methods used or a preponderance of more vulnerable groups in certain schools.

Prompted by the experience with tuberculosis in World War I, quick and eco-

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nomie means for examination of large groups have been developed, through photofluorography, miniature films and better technique for mass X-ray examinations (9, 21, 27, 33), during World War II (12). Practical methods are, therefore, available for examining large groups of the population (2, 9, 12) and mass surveys are already being conducted in industry and commerce (2, 9).

We have been passing through an era of rapidly changing opinions (14, 24, 26) on many phases of tuberculosis which have greatly influenced handling of cases. One by one, our criteria for diagnosis, prognosis and treatment have been discounted under scientific scrutiny and the development of new treatment measures (20, 25, 26, 30, 33).

More accurate methods and materials for tuberculin testing, and acceptance of X-ray evidence of the primary complex (18, 29) as specific for an early primary childhood type of disease, focused attention first on the child and led to the wholesale testing of grade school children; but similar tests of the young adult revealed less infection by puberty than had been expected and a mounting rate thereafter, while follow-up of grade school children disclosed a paucity of disease prior to adolescence. This directed attention from the child to the young adult (19, 21, 25) and eventually led to mass surveys in colleges and technical schools. Recent studies, however, have thrown grave doubt on the specificity for tuberculosis of the X-ray evidence of calcified hilar lymph nodes at any age (20), throwing doubt on our earlier statistics for both children and the young adult.

When collapse measures provided means for putting the diseased lung at rest and pulmonary resection succeeded in removal of part or all of the diseased organ, thus prolonging life for the more advanced case, the time-honored technique of early and prolonged bed-rest began to be replaced by these newer methods. However, the hailing of these procedures as a panacea for all tuberculous ills, led to a dangerous relaxation in the care of early disease through undue reliance on the ability of these measures to arrest more advanced disease later. The resultant procrastination in the early care of the minimal case in the young adult has jeopardized his best chances for early stabilization without advanced disease.

The influence of sex on the prevalence of tuberculosis is still controversial (16). Data to date support the claim of an earlier onset and earlier peak of mortality in women than men. Theories to account for this sex disparity on the basis of difference in occupation may be refuted when data are analyzed which are now being assembled in industry (2, 7, 16), where men and women are working side by side on the same job. An endocrine factor has never been disproved and is certainly suggested by the upswing in active disease after puberty, the increased pathological progress in the pregnant tuberculous woman (3), and an earlier drop in mortality at the climacteric in women than men. Till this has been clarified, early protection against the disease and routine observation by periodic physical and X-ray examinations are especially indicated for girls.

Comparisons of male medical students (22, 31) with students of nursing (19) are misleading because their average age and duties are not comparable. Not enough data are available on women medical students to date to warrant conclusions as to sex differences at the same age when subject to the same regimen.

It has been thought wise, therefore, to render a report of the experience at the only woman's medical school in America while developing a case-finding and follow-up program for the study of tuberculosis in women medical students (7, 19). It was planned to observe successive "generations" of students enrolling during about a decade, through their college life, and by correspondence or interview at intervals after graduation or withdrawal (6).

The objectives were to learn the amount of tuberculous infection and disease in the student body, the apparent points of greatest hazard, the types of disease encountered, its progress under medical school conditions, the adequacy of facilities available and the ultimate results. It was hoped that a control program to safeguard future generations of students against tuberculosis might evolve.

Unfortunately, the study paralleled a period of great unrest in the world, rapidly changing methods of medical teaching and practice and an entire reorganization and a complete change in administrative personnel in the institution being surveyed. The study originated in the Student Health Service whose Director was also the Professor of Preventive Medicine at that time.

This report is presented with the hope that, by an analysis of the mistakes and achievements of the project, it may be of some help to others facing the same problems in control of tuberculosis in medical students.

The general plan, as presented for adoption in 1932, in addition to the routine annual physical examination and urine and blood studies, was as follows:

- I. Tuberculin testing of all entering students, using the Mantoux method, to be repeated annually on all those with negative response, till conversion to positivity.
- II. Chest X-ray examination of all students at entrance and at least once yearly thereafter, with special X-ray films later as needed for confirmation of diagnosis and as a guide in treatment.

Upon the finding of evidence of infection or disease, the following regimen was recommended:

- I. Upon conversion to tuberculin positivity:
  - a. Student to be reassured and the meaning of the reaction and need for precaution explained.
  - b. Student to be warned against further known exposure and advised against early possible additional exposure in extracurricular work in hospital laboratories and clinics, so as to favor early stabilization without disease progression.
  - c. Student to be instructed to report promptly any altered physical state; especially loss of weight, anorexia, malaise, fever, cough, expectoration, night sweats, or sharp chest pains; and to report promptly for care of minor infections.
  - d. Student to be instructed to report for observation from time to time for recheck and further study.
- II. Upon development of suspicious signs and symptoms or suggestive X-ray shadows:
  - a. Student to be notified of possible early disease, reassured and her cooperation solicited in further study, as follows: (21, 23, 24, 25)
    - (1) To report for an early recheck physical examination and further X-ray films.
    - (2) To secure soon a blood test and sedimentation rate.
    - (3) To weigh herself weekly, on the same day and hour, for a prescribed time, and to report results.

- (4) To secure temperature readings morning and evening, daily at the same hour, and to report results, after a prescribed interval.
  - (5) If having cough and expectoration, to collect sputum specimen, in container provided, and take same to laboratory, where examination by stained smear, culture and guinea pig inoculation would be made.
  - (6) In absence of sputum, to report for aspiration of stomach contents for similar examination by the laboratory (5, 15).
- b. Student to be instructed to live as conservatively as possible during this study, to secure extra rest, maintain good nutrition and keep under close observation.
- (1) If case be minimal, with no signs or symptoms, to continue college work till completion of the disease study, reporting as above.
  - (2) If exhibiting suspicious signs and/or symptoms, or sputum examination reveals tubercle bacilli, to report to the hospital for bed-rest till completion of tests, or plans for withdrawal (14, 22).
- c. Student to secure early consultation, with:
- (1) A phthisiologist, preferably.
  - (2) Her family physician, if desired.
  - (3) Faculty clinician with experience with tuberculosis.
  - (4) Other consultant of choice.
- III. Upon confirmation of diagnosis:
- a. Student to be advised to withdraw at an early date for early treatment. (This gives the student her best chance for early recovery, with the least loss of time and with the least risk of further progress of disease, by removal from further exposure.)
- b. Management to be advised to require withdrawal: (22)
- (1) When signs and symptoms of active disease are demonstrated.
  - (2) When studies reveal tubercle bacilli in sputum or stomach contents.
  - (3) When progressing tissue changes are demonstrated by X-ray, regardless of other signs.

Some members of the Faculty and Management disagreed with item III of the proposed plan on the basis that, in their opinion, early withdrawal constituted too great a sacrifice for the student unless her presence in school could be proved to be a menace to others. Unfortunately, the Corporation lawyer rendered a legal opinion that proof of infectiousness by demonstration of bacilli in the sputum was necessary for requiring withdrawal of a student. Such proof is not readily demonstrated by direct smears; therefore, disease can progress and infection can be spread to others while waiting for culture and guinea pig methods to demonstrate tubercle bacilli (5, 15).

The program necessarily developed therefore on a compromise basis. Case-finding and follow-up for confirmation of diagnosis were carried out in the Student Health Service under the Professor of Preventive Medicine, as its Director, but the clinical decisions as to general medical handling, disposition of cases, basis of withdrawal of students and their return later were primarily under the jurisdiction of the Professor of Medicine guiding administrative policy by clinical advice.

Unfortunately, this method of dual supervision of student cases led to much confusion and contributed to progress of disease and to spread of tuberculosis to

others. Conflicting advice resulted which was due largely to honest differences of opinion as to the relative gravity of minimal lesions in the young adult in medical college (11, 22, 24), differing degrees of confidence in changing criteria for diagnosis of the "primary" "safe" case, and in faith in the adequacy of early ambulatory treatment (23, 33), relying on collapse measures to control conditions later. Too much responsibility was also placed on the student to regulate her own school life to meet the demands of so subtle a disease.

Decisions were colored, also, by administrative rules and regulations, designed to govern academic procedures, resulting in lay decisions on medical matters. Occasionally, advice of a family physician without full knowledge of the strenuous demands of modern medical education, or of a consultant, accustomed to deal with more advanced disease, led to delay in the care of early cases with progression of the process. A considerable amount of leniency developed on the part of the medical department and management, in permitting delay in withdrawal of students with early active disease with few signs and symptoms, and their return before full stabilization of their disease, in order to maintain their academic status.

The program evolved, therefore, slowly and somewhat painfully, by a system of trial and error, often meeting emergencies only after they arose. The following program eventually developed:

- I. Mantoux testing of all entering students began in the fall of 1932 and was repeated annually on all nonreactors till 1937, when a second test was added in the spring, to locate more accurately the time of conversion and as a guide to summer activities. Thereafter the test was made biannually.
- II. Stereoscopic 14 x 17" celluloid roentgenograms were made available in 1933, at the Phipp's Institute, at the student's expense, resulting in an incomplete student survey, especially of the busy upper-classmen. The following year, the same type film was procurable, at a prorated fee, again resulting in incomplete coverage of the student body.
- III. Flat 14 x 17" celluloid films were substituted for the above in 1935 for all students, at the College Hospital, each fall, routinely, as a screening procedure, with stereoscopic or other special X-ray examinations made available for study of suspected cases. In 1937 similar films were added in the spring for third and fourth year students, which were continued thereafter biannually, and in 1942 biannual films were begun for all students.

The survey eventually covered a period extending from 1932 to 1944. A total of 449 students were observed, including all those in residence at the beginning of the study and all newly matriculated students and transfers from other schools enrolling since. Students reëntering after absence or for repetition of work were included but once.

The students were under the observation of the writer, as Director of Student Health Service, until the spring of 1941. At that time, under a new Dean and a complete reorganization of the College and Hospital, the Student Health Service was transferred from the College to the Clinical Medical Department and became part of the Out-Patient Division of the Hospital. It was thereafter manned by

a relay of young clinicians under direction of the Dean and the Medical Superintendent of the Hospital. The students, thereafter, were not under personal supervision of the Professor of Preventive Medicine.

To complete the study, however, this report includes subsequent data obtained from review<sup>2</sup> of the Student Health Records, under new directorship, of those enrolled up to 1941 to their graduation or withdrawal in 1944. Data obtained by interview or correspondence with those who were under special observation for tuberculosis while in school, after their graduation or withdrawal, to learn the ultimate results of their experiences, are also incorporated in the report.

There was considerable overlapping in successive class enrollments which resulted in some variation in degree and duration of individual and class exposure. In addition, there was a difference in exposure while absent from school. A man-year basis for statistical computation was therefore considered impractical. In so small a series, also, rates have not been presented except in a few instances.

TABLE 1  
*Reactions to tuberculin in medical students entering in 1932*

CLASS	NUMBER	AVERAGE AGE	POSITIVE REACTIONS	NONREACTORS
First year .....	44	24 yrs.	58%	42%
Second year .....	40	24.2 yrs.	87%	13%
Third year .....	23	25.6 yrs.	90%	10%
Fourth year .....	30		100%	0%
School .....			83.7%	16.3%

The tuberculin testing (29) began in 1932 and followed the usual two-test technique advocated by the Trudeau Foundation and Phipp's Institute, Old Tuberculin being used until the Purified Protein Derivative was made available by Dr. Florence Seibert. Five millimeters or more of induration, regardless of erythema, was accepted as evidence of a positive reaction and indicative of infection, as advocated by these institutions.

Results of the first test of the entire student body, in 1932, appear in table 1.

Reactions obtained by single fall testing 1932-1937 and biannually thereafter are shown in table 2.

The gradual reduction, at entrance, of students with positive reactions during this period (16) seems to parallel the general downward trend in mortality rate in the general population and may indicate fewer open cases.

The rapid increase in positive tuberculin reactions (8, 17, 31) occurring in each class each year while in residence, however, strongly suggests a corresponding exogenous infection during the four years' exposure in medical school. This increase is at a somewhat more rapid rate than in men's schools.

The most rapid increase in infection occurred in the second half of the second

<sup>2</sup> These records have been reviewed for accuracy by the present Student Health Director.



year, prompting a search for hazards in that year's experience. Potentially, these existed only in laboratory and autopsy work and in contact with tuberculous patients for physical diagnosis demonstrations, since clinical work had not yet begun.

Early in the survey, 2 cases were discovered in laboratory personnel but they withdrew and no subsequent cases could be directly traced to them nor to the clinical or bacteriological laboratories.

The autopsy room at the large city hospital used for postmortem demonstrations presented conditions which were far from satisfactory. Efforts directed toward their correction subsequently resulted in installation of foot-controlled wash-basins for students, who had been using the same sink in which specimens were cleansed; establishment of a more rigid regimen of collection, sterilization and

TABLE 2

*Number and percentage of tuberculin reactions in 9 successive classes in a medical school*

ENTERED SEPTEMBER	AVERAGE AGE AT ENTRANCE	FIRST YEAR			SECOND YEAR			THIRD YEAR			FOURTH YEAR			DUE TO GRAD- UATE
		Number	Fall	Spring	Number	Fall	Spring	Number	Fall	Spring	Number	Fall	Spring	
1932	24	44	58%	No test	34	71%	No test	30	97%	No test	30	100%	No test	6/1936
1933	21	27	44%	No test	31	61%	No test	27	85%	No test	23	100%	No test	6/1937
1934	24	34	37%	No test	29	41%	No test	30	83%	No test	24	100%	No test	6/1938
1935	22	26	38%	No test	21	52%	No test	21	85%	No test	21	100%	No test	6/1939
1936	21	32	34%	No test	27	48%	No test	20	80%	95%	18	100%	No test	6/1940
1937	23	31	32%	No test	29	52%	95%	25	96%	100%	24			6/1941
1938	22	29	25%	40%	26	45%	80%	21	90%	100%	21			6/1942
1939	24	34	32%	51%	30	60%	61%	26	80%					6/1943
1940	24	34	26%	43%	36	53%	94%	*						6/1944
1941														

\* Records of Mantoux reactions after spring test of 1942 have not been presented, as having no bearing on the present report.

redistribution of soiled gloves, gowns and aprons, formerly taken to the students' respective rooms for cleansing; and reduction of time spent per individual student at autopsies. Significantly, the first class to have its autopsy service under this corrected regimen was the first, since the beginning of this study, to have no active tuberculosis cases in its membership by graduation.

Two students, after fixing and mounting pathological specimens, some tuberculous, during a summer vacation, developed pulmonary lesions by the following fall. One was accompanied by an unusually severe local reaction to the tuberculin test. In the other, a positive tuberculin reaction and X-ray evidence of a "healed primary complex" at entrance proved not to be reliable criteria for safe exposure.

No special method for determining possible spread from tuberculous cases used in physical diagnosis demonstration was applied in this study. Further investigation of this possibility is indicated, since the advanced case, the only one

presenting demonstrable physical signs, is potentially dangerous. Certainly, the most rigid protective regimen and its enforcement is indicated when open or advanced cases are used for demonstration in the early college years.

The time relation of tuberculin conversion to positivity and that of subsequent disease is important and is revealed by study of one group as shown in table 3.

Although a small series, this evidence supports the claim that recent sensitization predisposes to early disease. The conversion to positive tuberculin reaction, therefore, constitutes a warning against early secondary exposure, which is extremely useful as a protective measure in medical schools.

TABLE 3

*Tuberculous disease following conversion to tuberculin positivity*

NUMBER OF CASES OBSERVED	DEVELOPMENT OF DEMONSTRABLE ACTIVE TUBERCULOSIS AFTER TUBERCULIN CONVERSION TO POSITIVITY			
	Within 6 months	Within 12 months	In 12 to 18 months	In 2 years or more
38	22	12	2	2

TABLE 4

*Time relation of positive tuberculin reaction to development of disease*

	NUMBER OF STUD- ENTS	UPPER CLASSES AND TRANSFERS			DURING 1ST YEAR		DURING 2D YEAR		DURING 3RD YEAR	
		+at 1st test	+by 3rd year	+No test	+at en- trance	+by spring	+by fall	+by spring	+by fall	+by spring
Disease developing while in college.....	43	3	2	1	11	1	1	16	4	4
Disease progressing after college.....	13	6						2	3	2
Border-line without proved specificity...	19	1	1		4	1	3	5	1	3
Totals.....	75	10	3	1	15	2	4	23	8	9

The time when tuberculin positivity was first noted in 75 students watched for demonstrable or suspected disease is shown in table 4.

In section work in clinics and hospital service where active tuberculous patients may be encountered, recent conversion to tuberculin positivity should constitute the guide in section assignments and as long a time as possible should elapse between the tuberculin conversion and such subsequent exposure, to avoid overwhelming the body defense mechanisms.

A number of students, revealing by X-ray at entrance evidence of "healed primary disease," were negative to the tuberculin test (20). If this X-ray evidence can be accepted as specific for earlier tuberculous disease, we must assume that, should any degree of immunity survive the loss of allergy, it certainly is not sufficient to protect against exposure in medical school, since all students were reconverted to positivity while in college.

We had been interpreting this phenomenon as indicative of loss of allergy, following complete neutralization of the tuberculo-protein of destroyed bacilli of an earlier infection, with termination of the disease process. However, we lack satisfactory scientific proof of this theory and, if recent work (20) indicating that calcifications in hilar lymph nodes are not always caused by tuberculosis be proved, we must revise our concept of "primary" and "secondary" disease. In any event, such evidence cannot serve as a criterion for safety in further exposure to known tuberculosis.

Tuberculin positivity (29) *per se*, being an evidence of infection and allergy only, cannot be interpreted as indicative of immunity nor a criterion for further safe exposure. Neither can a recent conversion to positivity in the young adult be accepted as proof of a primary process of potentially mild type, even in the absence of hilar shadows; it is rather a warning index against early additional exposure.

An analysis of 56 case histories of the students who developed active tuberculosis during this survey has been made. Active disease developed in 43 of these students while still in school. After leaving college, 13 developed disease or gave evidence of progressing activity.

There were also observed for possible tuberculosis 19 further students who were never proved tuberculous by demonstration of the tubercle bacillus, and, as far as known, never progressed beyond the first minimal suspicious stage, the so-called "pre-phthisical tuberculosis" (23). These, together with those showing evidence of healed parenchymal lesions which remained quiescent, and cases showing X-ray evidence only of the primary complex were excluded from the analysis.

The students with active disease experienced all degrees of involvement, with varying amounts of spread, complications and healing (30). The type of disease ranged from the minor, minimal, asymptomatic case without physical signs, showing minor spread by X-ray only, to far advanced disease with many complications. The course of the disease ranged from the slow insidious chronic case, running a number of years before stabilizing, to the quickly fulminating fatal case, now rare in the white race. Although none died while in school, 6 later progressed to a fatal issue, 2 within a year of onset.

The analysis revealed an unusual development of fairly well advanced disease while still in school, resulting from delay in their withdrawal. This justified the recommendation for early withdrawal which was part of the originally submitted plan to be incorporated into the Control Program.

Certainly, such treatment provides the best chance for quick stabilization of the minimal lesion with the least loss of time, away from an infective environment, with the least danger of advanced disease (31).

There also was a tendency to delay sanatorium treatment after withdrawal until complications required collapse therapy, emphasizing the fact that the gravity of the early lesion has been falsely minimized by undue confidence in the ability of collapse measures to control all more advanced disease. This occurred in 8 cases in this series, all of whom eventually ran a protracted course with complications. The importance of early rest treatment to prevent complications and as an adjunct to other procedures is not sufficiently appreciated.

Students also tended to attempt to resume college work before complete stabilization of their tuberculosis. Of 29 students returning after treatment, 13, or 45 per cent, later relapsed. Responsibility both for delay in seeking treatment and for returning too soon must be shared by family physicians, consultants, college officials and students.

Patients remaining in school after diagnosis and returning after treatment brought the number of tuberculosis cases currently "in residence" during individual years to a level not consistent with true current disease prevalence and raised morbidity rates for the school and the current classes. This pyramiding of cases was especially noted during 1937, 1938 and 1939 while absorbing "carried over" and returning cases from previous years (22), which practice prevailed at that time, as the then current policy of the medical department.

These retained and returning cases, furthermore, kept active cases in the class-rooms to infect others. Several "chains" of such contact cases among students were noted, occasionally running through several "generations" of students. One case returning with unstabilized disease lived with a fellow student, who, in turn, lived with a friend and later with another student, all successively developing active disease. The last mentioned, later returning unstabilized, completed her college work but relapsed as an intern, further exposing fellow-interns and patients while remaining on part-time duty under observation, awaiting results of laboratory tests which eventually disclosed tubercle bacilli.

The housing situation presented grave problems also. A legal opinion was rendered by the Corporation lawyer that the College could not dictate regarding places of residence for paying students unless it provided living quarters, thus nullifying college control of housing conditions contributing to spread of disease. In one instance, 4 cases of active disease developed successively in students living in one house where the landlady was suspected of having chronic tuberculosis, but whose doctor, without current X-ray or sputum examination, reported her as negative for tuberculosis. Her offer of free room in exchange for the students' presence at night prompted the girls to live there, despite warnings. Disease spread directly from this group to 3 others. Twenty years have been spent by this group for recuperation, 2 have permanently withdrawn, and 2 are not yet fully stabilized.

During the first four years of this survey, when routine roentgenological study was not available, a high incidence of moderate and far advanced disease at the time the diagnosis was made and rapid progress of disease in those remaining in school might be expected. In 181 students observed during that interval, 18 developed disease, 50 per cent of whom were first diagnosed by signs and symptoms. Three only were arrested in the minimal stage, 2 permanently withdrew, 3 died and forty-seven and three-fourth years were lost for treatment. This constituted a major challenge for further investigation and demonstrated the urgent need for a control program.

X-ray evidence at time of diagnosis is not, *per se*, a reliable index of activity. Hilleboe (9) states, "as desirable as it may be to determine the exact pathological nature of a lesion by X-ray alone, histologic roentgen diagnoses are always based on extremely indirect evidence and therefore are unreliable." Nevertheless,

by an analysis of cases, comparing subsequent studies and developments with earlier roentgenological evidence, valuable data are revealed which may aid in earlier diagnosis and more accurate prognosis in future cases (24).

Very light flocculent shadows of limited extent, usually in the upper lung fields, were, in these young subjects, found to represent early minimal lesions. In most instances, they were accompanied by mild or no symptoms and tended to clear or stabilize promptly on early withdrawal with a short rest period, leaving light linear shadows or no evidence. Of 14 such cases, only 6 proved reversible. In 4 cases recently allergized, with no evidence or history of previous disease and with ultimate complete disappearance of X-ray shadows, "epituberculosis" (32) with edematous exudate of allergic origin or patchy atelectasis was thought to account for the X-ray shadows. However, the assumption that all these lesions, in recently allergized students, "being primary, will heal spontaneously" was found to be far from warranted. When remaining in the hazardous environment of medical college, these students may be overwhelmed by added infection and progress fairly rapidly to an advanced stage of disease needing prolonged care. Eight cases had such unfortunate experiences. The early minimal lesion is very apt to be minimized in importance by clinicians accustomed to more advanced disease. It, however, needs especially careful watching in medical school, frequent rechecking and immediate withdrawal of the student to a safer environment at the first sign of spread—the most difficult student cooperation to secure.

In the mixed exudative-productive type (24), the prognosis may be more definite. Healing has begun and often may continue, at times simultaneously with a slow spread at other points, often running a very chronic course but tending to heal. At any time, however, following a minor illness, an exhausting experience or an added exposure, the exudative process may outstrip the fibrosis. Therefore, this type also needs careful watching and best results are obtained by continuing treatment till fibrosis is well advanced. Two cases in this group illustrate the favorable and 4 cases the unfavorable course in this type; 2 of the last group completed their college work apparently well controlled but relapsed after graduation.

Calcified parenchymal lesions, except so-called Ghon foci, were uncommon in these young adults and, when found, were not extensive. The mistaking of a caseous nodule of unusual size and density for a calcified lesion was made twice in our series by clinicians and roentgenologists. In each instance, subsequent liquefaction, excavation, positive sputum and a febrile course ensued.

One factor, very frequently responsible for delay in diagnosis and treatment, was the masking of the early lesion by the roentgenological picture of recent, prolonged or repeated upper respiratory disease (10). The associated increased bronchovascular shadows may readily obscure the lighter early tuberculous shadows. Sinusitis is the most frequent interpretation made of this type of roentgenological picture. Clinicians frequently differed in their interpretations of minimal shadows accompanied by mild fever, anorexia, loss of weight or increased sedimentation rate, often resulting in delay till advanced tuberculous disease developed. One patient with exudative-productive lesions, exhibiting fever, cough,

loss of weight, malaise and anorexia, was diagnosed by the clinical consultant as chronic sinusitis, despite a familial history of tuberculosis, a positive Mantoux reaction at entrance and demonstrable râles. The disease progressed very slowly till after an acute exacerbation of the upper respiratory infection, when it progressed to a bilateral lesion and cavitation with positive sputum. This student ultimately withdrew twice before recuperation.

Ten cases were delayed by diagnoses of upper respiratory infection by clinicians and the X-ray evidence interpreted by the roentgenologist as "of no present significance." In retrospect, after development of more advanced disease, these same pictures were found to have shown "early evidence of tuberculosis" (24).

Other coincidental diseases of a chronic nature, with symptoms common to early tuberculosis, also presented problems and interfered with early diagnosis and treatment.

One diabetic (1) student, under the care of her own physician, progressed to cavitation, laryngeal ulcer and toxemia late in her senior year, early evidence being attributed to the diabetes. Another, with endocarditis, also developed advanced disease with cavitation in her senior year, continued the year with the help of pneumothorax, but lost two years for stabilization. Three cases with history of rheumatoid arthritis exhibited recurring attacks of migratory pain and, when pleurodynia ushered in a tuberculous process, it was considered part of the rheumatoid picture.

Pleurodynia was a very common early warning symptom in this series. However, since the symptom appeared very early, often before X-ray evidence of disease, its significance was not at first appreciated. History of such symptom was elicited in a large proportion of our cases at some time early in the course of the disease. Warned by this symptom, frequent X-ray films may reveal a lesion at a very early, reversible stage. Massive pleural effusions were primary in 3 patients and secondary in 4, all preceded by pleurodynia.

In this series of cases, pneumothorax was resorted to in 24 students, in 4 of whom selective bilateral treatment was necessary. Pneumonolysis was required in 4 cases and twice phrenic nerve surgery was thought necessary.

One case of primary tuberculous rectal fistula was accompanied by a secondary minimal parenchymal lesion which cleared promptly upon surgical extirpation of the fistulous tract.

Active disease usually developed near the end of the college year, except when previously diagnosed cases were kept in school and progressed early in the subsequent year. They frequently became active after the usual annual increase of upper respiratory infections or following special strains, such as out-practice service or academic examinations, emphasizing the rôle of superimposed infection and fatigue in activating tuberculous disease. Except when students in the pre-clinical classes were intimately exposed to active cases allowed to remain in school after diagnosis or readmitted before complete stabilization, those infected during the first two years did not frequently develop disease till the clinical years. Presumably, clinical contacts then added overwhelming exogenous infection or fatigue favored development of disease.

A notable exception to this rule, however, occurred in the spring of the college-year 1941—42, when the Student Health Service was transferred from the College to the Hospital. A 56 per cent increase in tuberculin reactions occurred in the second year class at the spring biannual test and, soon thereafter, an unusual number of very active cases of acute tuberculosis developed in the class. In 36 members of the class, 27 entered as first-year students in 1940 and 9 were repeating. In the former, 7 cases of active disease developed and in the latter, 3, a total of 10 in the class. Progression of disease in this group was unusual. Six of the students ran a rapid course not common to-day in the white race, with very early spread and early complications. Two of them have since died, one within a year of onset. That spring, an unusual number of very severe local reactions to the tuberculin test, in both of the preclinical classes, had also been noted (11,28).

Data relative to this episode appear in table 5.

A common source of unusual exposure was sought in diseased students and faculty personnel or in contact with special clinical patients, but no source common to the entire group could be located. In absence of proof to the contrary, therefore, it seems logical to conclude that an unusual exposure, not officially realized, existed in the transfer of the Student Health Service headquarters from the Department of Preventive Medicine, with its safer location in the College building under close observation, to the more exposed environment of the Out-Patient Department of the Hospital with shorter clinic hours for students, longer waiting periods and a relay of physicians. Young students in the preclinical years were thus exposed, unusually early, not only to casual contact with routine clinic patients, but intimately to tuberculous patients visiting the city chest clinic, which unfortunately was situated directly across a narrow corridor from the student dispensary, the patients from both clinics using the same waiting benches.

In addition, the second year students were further exposed the same year to the hazards of the autopsy service. This dual exposure, in rapid succession, could readily overwhelm the defense mechanisms of the bodies of those who developed early disease and allow for the rapid progression to moderate and far advanced disease of the 6 fulminating cases.

Following this experience, a special committee, made up of representatives of the medical schools who used the autopsy service of the same hospital, compiled a set of very rigid rules regulating autopsy room procedure which was presented to the hospital management. Upon their adoption, the College appointed a member of the Pathology Department to instruct and observe the students, to superintend the transfer of tissues and organs from the autopsy room to the College and to be responsible for the fixing of the tissues.

Since adoption of this new regimen and transfer of the Student Health Service clinic back to the College building, it is significant that new cases of disease have been spectacularly reduced. Only a few minimal cases have developed and those have been stabilized with little extension. A few cases, returning from earlier years, have relapsed, however.

**TABLE 6**

*Data on 10 cases of tuberculosis developing concurrently in a class of women medical students in second college year*

**A. Tuberculin sensitivity and extent of lesion at diagnosis**

	ENTERING IN 1940	REPEAT- ING	TOTALS	MORBIDITY RATES	TUBERCULIN REACTIONS								X-RAY EXTENT AT DIAGNOSIS		
					Entrance		Spring '41		Fall '41		Spring '42		Unilateral	Bilateral	Total Minimal
					-	+	-	+	-	+	-	+			
In class.....	27	9	36	27%	27	9	20	10	17	19	2	34	7	3	10
Tuberculous cases.....	7	3	10	33%	9	1	9	1	9	1	0	10	7	3	10

### B. Development of X-ray and physical signs and symptoms

	EXTENT OF LESION			PROGRESSION				PLEURISY			EMPHYSEMA		GENERAL SYMPTOMS			CAVITY		ADENITIS		ULCERATED LARYNX
	Min.	Mod. adv.	Far adv.	Unilateral	Bilateral	Total spread	Resorption	Stabil.	Pleurodynia	Adhesions	Effusion	Intrapulmonary	Intrasternal contents	Fever	Wt. loss	Sed. cl.	Unilateral	Bilateral	Illar	
At diagnosis.....	10	0	0	7	3	10			7											
Extension																				
Early.....	6	4	0	3	4	7	3	3		2	1	2	2	4	4	5	1	1	1	
Later.....	4	2	4		6	6	2	2			1	2		6	6	?	1	1		1

### C. Disposition of cases and final results

[illegible]



More recently, an advisory committee of clinicians experienced in tuberculosis has been appointed to review student cases with the Director of Student Health to facilitate prompt diagnosis and early treatment and to evaluate the degree of stability of those returning after treatment.

A very similar episode (28) to that just related occurred at a mid-western medical school in 1944, where an unusual number of tuberculous patients examined at autopsies attended by the students and the use of tuberculous cases for the demonstration of physical diagnosis were held responsible for the unusual exposure (11).

Evidence to date certainly points to the fact that at least one serious source of tuberculous infection for medical students lies in their participation in autopsy procedures on tuberculous cases and in attendance at prolonged sessions in the autopsy room. In large city hospitals, however, where the number of tuberculous patients is high, and where large numbers of cases come to autopsy daily, it is very difficult to guarantee safe conditions by simple hygienic measures practiced by individuals. The hospital is responsible for rigid rules to cover environmental sanitation. Proper installation and use of equipment for irradiation (13) of the premises would contribute to the safety of all concerned and should be a worth while investment for these institutions, to preserve the health and usefulness of their young interns and residents. Further danger lies in too early exposure of young students to patients with active tuberculosis.

Fifty-six active cases of tuberculosis in 449 medical students in twelve years resulted in 6 deaths and, for an appreciable number of others, in long periods of semi-invalidism while attempting to regain their health, leaving some still incapacitated. An infection rate of 100 per cent, X-ray evidence in 16.7 per cent, a clinical morbidity rate of 12.5 per cent, a case-fatality rate of 10.7 per cent and a mortality rate of 1.3 per cent, developing in a stronghold of medicine with facilities readily available, certainly constitutes a challenge of sufficient magnitude to interest the entire medical profession in a survey of conditions in other medical educational institutions and hospitals.

The ultimate cost in personnel lost from the profession, in time spent in recuperation (more than 100 years in this small group), in actual monetary expenditure and disappointment and embitterment of those who have had their life plans thwarted and have been obliged to change to other vocations, makes this not only a grave medical but a serious social problem.

The control of this hazard in medicine, as in other hazardous occupations, lies, first, in finding the hazard; next, in removal of the hazard at its source; in preemployment examination for proper placement; in periodic examination to determine the effect of the hazard; in early removal of the worker from the harmful environment; his prompt and adequate treatment; and his safe rehabilitation for return to duty (16).

The responsibility for solving its own problem rests first on medicine and especially on its medical educators. The financial burden falls eventually on the public who must pay, in tax-support, for medical schools and hospitals, for the care of the tuberculous in sanatoria, and for Public Health Services to find and

follow up the cases. Unless this responsibility is recognized and assumed by the profession, then, as has happened in some states, we may expect medical schools and hospitals to be made responsible, under compensation laws (16), for tuberculosis as an occupational disease.

Eventually, most of the aims and purposes of the originators of the project herein reported have been accomplished, but by a system of trial and error and at much too high a price. The originally proposed plan, when finally adopted in entirety, has proved effective. In the past few years, a few students have reached graduation still tuberculin-negative, showing a slight lessening of new infection and sensitization; a few minimal cases only have developed in the past three years, suggesting a lessened amount of superimposed infection; and progression in these few cases has been limited and promptly stabilized by earlier care. The program should be continued, expanded to include a search for disease in all college and hospital personnel, including all patients, and their follow-up; and the plan should be extended in its application, in principle, into the intern and resident services. With some such program put into universal practice in all medical schools and hospitals, the medical profession may eventually solve its own disease problem and make its training period a safely regulated, even though an essentially hazardous, experience for its young acolytes (31).

It will require, however, the hearty coöperation of all personnel in medical colleges and hospitals, and the loyal support of medicine and the public whom it serves.

#### CONCLUSIONS

Tuberculosis is to date the major occupational disease hazard of the student of medicine, during undergraduate and early graduate years.

Infection with tuberculosis takes place readily in the medical school, chiefly in the preclinical years, and disease may follow during the clinical or postgraduate training periods.

Disease occurs earlier and progresses more rapidly in women than men; hence, tuberculosis will be found more frequently during medical school years in the former and must be sought especially through the intern and resident years, as well as in medical school, for the latter.

Autopsy service and the use of tuberculous patients in demonstrations for physical diagnosis and clinical training constitute the chief sources of infection in routine medical school procedures.

Where there is lack of appreciation of the gravity of tuberculous disease in the young adult, reliance on doubtful or controversial criteria for diagnosis and prognosis, or undue confidence in later application of collapse therapy, delay in diagnosis and treatment may readily result, with increased danger to the student.

When withdrawal of diseased students is delayed or students return before full stabilization, disease progression, relapse and spread to others, by student-to-student contact, may be expected.

The ultimate cost of tuberculosis to the student, in time lost, expense of treatment, sacrificed career or even life; to the medical school, in wasted educational

efforts; to the profession, in loss of promising future physicians; and, indirectly, to the public, is far greater than generally realized.

Development and operation of an adequate control program against tuberculosis in medical schools and hospitals is imperative. This should include case-finding and follow-up programs in medical schools; establishment of safer techniques in autopsy rooms, laboratories, clinics and wards of hospitals; obligatory entrance and periodic examinations of interns and residents, including X-ray examinations; early care of all tuberculous patients; and routine examinations of all college and hospital personnel, including ambulatory and bed patients.

Responsibility for safeguarding students and graduates of medicine against tuberculosis rests with the medical profession. Unless this is realized and responsibility assumed, compensation laws covering tuberculosis as an occupational compensable disease, already existent in some states, will probably become general.

#### SUMMARY

A report of a case-finding survey and a follow-up program in a group of 449 women medical students has been presented.

The incidence of tuberculosis over a period of twelve years has been determined and 56 cases of disease have been summarized and analyzed.

Modes of infection, transmission, disease development, prognosis, progression and final results in this group have been considered.

An attempt has been made to locate the points of greatest hazard and to determine the underlying reasons for the incidence of disease in women medical students in this institution, with a view to their correction.

The need to safeguard future students, interns and residents during training years has been emphasized and the rôle of the medical profession in such protection has been pointed out.

A plan, found effective for undergraduate training years, has been proposed, with recommendations for its extension into intern and resident training periods and for case-finding and follow-up of all hospital and college personnel, including ambulatory and bed patients.

#### SUMARIO

Este informe describe una encuesta para el hallazgo de casos y un plan de observación subsecuente en un grupo de 449 mujeres que estudiaban medicina.

Se determinó la incidencia de la tuberculosis en un período de 12 años y se sumarian y analizan 56 casos de enfermedad.

En este grupo se consideraron los modos de infección, transmisión, desarrollo de la enfermedad, pronóstico, avances y resultados finales.

Se trató de localizar los puntos de mayor peligro y de determinar las causas subyacentes de la incidencia de la enfermedad, en las estudiantes de esta institución, a fin de corregirlas.

Se hace hincapié en la necesidad de proteger a las futuras estudiantes, internos y residentes, durante los años de entrenamiento, así como también se señala el papel de la profesión médica en dicha protección.

Propóneose un plan que resultó eficaz durante los años de preparación profesional, recomendando su extensión a los períodos de adiestramiento de internos y residentes y para el hallazgo de casos y observación subsecuente de todo el personal del hospital y la universidad, incluyendo los enfermos ambulantes y de cama.

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## TUBERCULIN REACTORS

### An Interpretation and Evaluation of Certain Data

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Tuberculin, one of the most valuable biological diagnostic tests available, has suffered many unjust critical condemnations probably because of the vagueness of the understanding of its mechanism and the overenthusiasm created by its spectacular performances, which have led speculative enthusiasts to attribute almost unnatural powers to it. Briefly, thus occurred its failure as a cure for tuberculosis, the basis for the explanation of specific immunity, its value as a therapeutic agent, its basis as an explanation for the toxemia in tuberculosis and its rise even in nonspecific amounts to buoy up the erroneously pronounced conception that all adults have tuberculosis and the infection occurs in the cradle. On this basis, the dictum was even proposed that tuberculin tests are valueless in adults. No truer words were expressed than the statement by Long, early in his studies on tuberculin, that tuberculin is a relatively specific agent only and is to be used with this in mind.

Thus even modern tuberculin testing for diagnosis is suspected of being valueless because of the high incidence of nontuberculous positive reactors, because it does not yield 100 per cent positive results in individuals with diagnosed tuberculous disease and because it does not correlate with nonspecific diagnostic findings, such as those obtained by the methods of roentgenology, physical examination and even some findings at postmortem examination. However, little heed is given to the facts that no biological test is perfect and that other verifying observations are essential to an efficient evaluation of a patient. It would be equally unjust to claim that the tubercle bacillus is not the cause of tuberculosis because we fail to find the bacilli by bacteriological technique in certain obvious tuberculous cases during life and particularly at times at the postmortem table.

As late as 1941, Savage (1) tested different tuberculins in the same individual and indicated a "marked variation in the response to these preparations has been observed," and, "a greater number of reactors to one preparation has been demonstrated." He finally concluded, "In so far as detecting clinically significant lesions is concerned, all preparations appear to be of equal value." It is to be noted that, with the use of the Mantoux and other tuberculin tests in case-finding surveys, the number of reactors in itself is not significant so long as the clinical tuberculous disease is discovered.

Contrary to this viewpoint is that of a school of thought which stresses that the reliability of a tuberculin test is based entirely on the greater number of positive results obtained without relationship to the clinically significant cases. Typical of this school is a recently published paper by Holden (2) in which a comparison

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is made between the intracutaneous (Mantoux) and transcutaneous (Corper) tuberculin tests as employed in a case-finding survey. The literature cited therein (3, 4, 5, 6, 7, 8) reports that both the two-dose intracutaneous (Mantoux) and the transcutaneous (Corper) tests result in high percentages (90 to 98 per cent) of reactors among persons with clinically established tuberculous disease. In respect to the single dose (PPD), Long (3) claimed a 94 per cent reliability, Stiehm (4) 77.5 per cent, and Narodick (5) 68 per cent. In a study on 508 persons at a detention institute, Long *et al.* (9) found 278 reactors to the two-dose PPD test. In the same study, of 54 with diagnosed tuberculous disease, PPD<sub>1</sub> picked up 78 per cent, whereas the complete two-dose test revealed 93 per cent. Since the single dose Mantoux (PPD<sub>1</sub>) test evidences a lower percentage (about 75 per cent) of reactors with diagnosed tuberculosis, its reliability as a screening test for the disease is considerably less than the two-dose intracutaneous test.

In the opinion of Furcolow *et al.* (10), an intermediate PPD dose of 0.000,1 mg. would screen out all persons with tuberculous disease. They also consider doses above this amount to give nonspecific reactions. It should be stressed, therefore, that the PPD<sub>2</sub> dose of 0.005 mg. (which is fifty times that recommended by Furcolow for test) produces a high number of nonspecific reactions. While PPD<sub>2</sub> will screen out active tuberculosis missed by PPD<sub>1</sub>, it will at the same time give a far greater number of tuberculin reactors among individuals with or without tuberculous infection who definitely have no diagnosable tuberculous disease. Because of this large number of reactors, the two-dose intracutaneous technique loses its efficacy for case-finding surveys. It is important to distinguish between reliability and efficacy.

The tuberculin test is a screening technique for reactors, hence some supplementary diagnostic means must be employed to determine which among the tuberculin reactors have tuberculous disease. Although the two-dose (Mantoux) technique is reliable, inasmuch as it will contain almost 100 per cent of cases with tuberculous disease within the reactors, it is not as advantageous for survey purposes as either the intermediate intracutaneous or the transcutaneous techniques. The latter will be as reliable as the two-dose test in picking up almost 100 per cent of cases with tuberculous disease but will, at the same time, show a much lower number of tuberculin reactors. Even where it is desired to screen out the tuberculin (tuberculo-allergic) reactors for purposes of considering possible tuberculous contacts, the intermediate intracutaneous technique is preferable to the two-dose test, inasmuch as the former will probably pick up most of the specific tuberculo-allergic persons yet eliminate the nonspecific tuberculin reactors which would be present with the two-dose test. The use of tuberculin testing for this purpose is distinctly different from that of case-finding surveys, and this problem will be discussed later.

In the present state of tuberculin testing, none of the techniques employed will give an absolute 100 per cent screening for tuberculous disease. There is some small percentage of cases with tuberculous disease which will give a negative tuberculin reaction even with the high dosage of PPD<sub>2</sub>. The clear explanation for this failure is still to be sought. This is probably inherent in the mechanism

of the reaction, which is itself not understood too clearly at present, and hence interfering conditions have escaped satisfactory explanation. Different tuberculin testing techniques depend fundamentally upon the same basic reaction mechanism, and consequently biological discrepancies would have a common underlying explanation.

Holden (2) checked 1,599 students by means of the transcutaneous test, employing autolytic tuberculin. Simultaneously, 811 of these students were checked by the intracutaneous test (either two-dose or intermediate) employing PPD prepared from the same bacillary culture used to obtain the autolytic tuberculin. Thus only slightly more than half of the students received simultaneous testing by the intracutaneous technique. Of the 811 students receiving the intracutaneous test, 518 received the intermediate and 293 received the two-dose test. It is not considered desirable to evaluate the transcutaneous (Corper)

TABLE 1

TEST	NUMBER TESTED	NUMBER POSITIVE	PER CENT POSITIVE
1. Transcutaneous (Corper).....	788	175*	22.2
2. Transcutaneous (Corper).....	518	54	10.4
Intermediate (Mantoux).....	518	65	12.5
(0.000,1 or 0.000,2 mg. doses)			
3. Two-dose (Mantoux).....	293	123	43.3
(combined PPD <sub>1</sub> and PPD <sub>2</sub> )			
Transcutaneous (Corper).....	293	62	21.2
(combined TT <sub>1</sub> and TT <sub>2</sub> )			

\* This includes 35 cases which gave simultaneous positive and negative reactions.

technique as compared with the standard two-dose intracutaneous (Mantoux) test on the basis of 293 simultaneous tests out of 1,599 students tested in which no case of clinically significant tuberculosis was found in the entire series. Table 1 summarizes the data presented by Holden (2).

The conclusion drawn from the data presented in table 1, namely that the two-dose technique is the more desirable one because it gives a higher percentage of positive results, is completely erroneous. Such a technique is precisely the one to be avoided in case-finding surveys because of the possible higher percentage of reactors among persons without tuberculous disease. If one bears in mind the distinction between reliability based on tuberculous disease as contrasted with the meaningless reliability based on high numbers of reactors, and also the distinction between reliability and efficacy, it then becomes quite clear that the technique which gives the minimum number of reactors among persons without tuberculous disease should be considered the most suitable. The intermediate intracutaneous and the transcutaneous tests compared favorably with each other in this respect on the group of 518 persons tested simultaneously with these techniques.



In the group of 293 students checked simultaneously by the two-dose intracutaneous and by the transcutaneous tests, the TT<sub>2</sub> test depended on initial screening by PPD<sub>1</sub>. Statistically, an entirely different result would be obtained if the initial screening were based on TT<sub>1</sub> negative tests instead of PPD<sub>1</sub> negative tests. While it is obvious that the statistical basis for the comparison reported on this group of 293 students is in error, the more serious error lies in the attempt to evaluate a survey test solely on the basis of number of reactors. The discrepancies and inconstant results reported by Holden (2) arise from the faulty method of screening as indicated above. No attempt was made to determine possible discrepancies for PPD<sub>1</sub> either on recheck or on simultaneous tests on the same person. The explanation for such discrepancies may be in any number of conditions—those inherent in the mechanism of the reaction, in lower grade allergies, in varying conditions of the test, including errors in technique, in anergic conditions, in nonspecific reactions, in interpretation of border-line results, etc. However, these discrepancies, whether they be found in autolytic

TABLE 2

METHOD	REACTORS* IN PER CENT	TUBERCULOUS DISEASE† IN PER CENT
PPD <sub>1</sub> (0.000,02 mg.).....	11.7	75
PPD intermediate (0.000,1 or 0.000,2 mg.).....	11.6-13.7	95
PPD <sub>2</sub> (0.005 mg.).....	43.3	95
Transcutaneous.....	9.8-19.9	95

\* Holden (2).

† Stiehm (4), Narodick (5), Corper (6), and Long *et al.* (9). Percentages are approximate.

tuberculin, in PPD, or in various grades of OT, as previously pointed out by Savage (1), have little significance in evaluating the reliability of a survey test, since in most cases they would not occur in persons with tuberculous disease.

Table 2 shows a comparison of the reactors and tuberculous disease picked up by the different techniques discussed. It is evident that the number of reactors obtained is of little consequence so long as the technique reveals close to 100 per cent of cases with tuberculous disease.

The following criteria are recommended for a suitable tuberculin test to be employed diagnostically in case-finding surveys. These criteria are limited to tests to be used for this purpose only. (a) The test should reveal as close to 100 per cent as possible the number of cases with active tuberculosis, verifiable by clinical and other diagnostic means; (b) the test should give a minimum of tuberculin reactors among persons without tuberculous disease; (c) the test should lend itself to ease of administration, it should cause minimum discomfort to the patient, it should be readily interpretable and give reliable results, it should be of minimum cost and time duration. When dealing with large numbers

of persons, as is intended in the use of any test for survey purposes, the above factors assume considerable importance. Most of the confusion and argumentation relating to the number of reactors desired in a tuberculin test has been occasioned by a misunderstanding of the use to which such a test is to be put. An entirely different problem confronts us in the use of a tuberculin test for purposes of screening persons who may have a tuberculous infection but do not have any verifiable tuberculous disease.

Such a tuberculin test must meet two conditions: (a) It should detect to a high degree the specific tuberculo-allergic individuals, that is, the test should be reliable and sensitive enough to pick up most of these allergic individuals, including those with low grade allergies; (b) it should give a minimum of non-specific reactions. No intracutaneous dose has as yet been established, despite the claims made for PPD, which will meet these two conditions. As Furcolow (10) indicated, the intermediate intracutaneous dosage comes closest to meeting condition *b* with a probable satisfactory reliability. Holden (2) has shown that the same considerations apply to the transcutaneous test. The fact is generally accepted to-day that given a large enough intracutaneous dose a positive reaction will be obtained in almost all persons. The factor accounting for this greater percentage of reactors is that of nonspecificity. Thus, even for infection surveys, the fallacy of seeking the highest number of reactors without regard to the question of nonspecificity should be obvious. It should be noted, as pointed out by Long *et al.* (9), that the danger of severe reactions is always present with the use of initial intracutaneous PPD doses larger than 0.000,02 mg.

Two major types of nonspecificity must be recognized in the use of tuberculin reactions. The OT employed prior to the establishment of standard PPD contained the element of nonspecificity due to reactions occasioned by extraneous materials present in the tuberculin preparations. As Long *et al.* (9) stated, "When OT is used in high dilution the effect of these extraneous constituents is probably negligible, but the concentration of these substances in the higher doses often used is certainly such as to raise some question as to the specificity of reactions secured." There is no room for argument that PPD eliminates this type of nonspecificity. However, these same authors in establishing a PPD<sub>2</sub> dose selected that amount of PPD (namely 0.005 mg.) which gave correlating results to OT. In 1,902 persons they found 65.3 per cent reactors to OT (final dose 1.0 mg.) and 65.8 per cent reactors to Purified Protein Derivative (final dose 0.005 mg.).

There is no reason to expect that, whereas nonspecific reactions are present with OT, none are obtained with PPD for correlating percentages of reactors. The specificity of PPD has been based on animal studies in which normal animals never gave a positive reaction. The fact has been seriously neglected in this conclusion that such animal studies are not appropriate for evaluating specificity since normal (confined) animals have no opportunity of acquiring the nonspecific type of allergy to any greater extent than that of tuberculo-allergy. In free roaming animals, there is a type of nonspecificity, due perhaps to other acid-fast organisms as recognized by Long *et al.* in cattle, which must be taken into account

in the interpretation of tuberculin reactions. This type of nonspecificity in man no doubt is responsible for the greater proportion of increasing numbers of reactors with increasing doses of PPD. Hence the number of reactors in any tuberculin testing must be interpreted with caution.

We agree with Long *et al.* (9) that "it is obviously impossible to determine in living human beings if any type of tuberculin is a perfect detector of tuberculous infection."

With the data available to date regarding reactors, it is only possible to conclude that tuberculin testing is quite adequate for case-finding surveys but must be used with extreme caution for purposes of screening persons with the infection.

#### SUMMARY

1. Tuberculin testing for diagnostic case-finding surveys has proved itself reliable by intracutaneous (Mantoux—with proper amount of tuberculin) and transcutaneous techniques (Corper).

2. An interpretation of the significance of reactors and the relation to non-specificity are presented. The fallacy of evaluating tuberculin tests on the basis of high numbers of reactors is expounded. For case-finding surveys, the test which elicits the minimum number of reactors among persons without tuberculous disease is the superior test.

3. A set of criteria based on efficacy as well as reliability is recommended for acceptable tuberculin testing programs.

#### SUMARIO

1. La comprobación con tuberculina para el descubrimiento de casos en las encuestas ha resultado fidedigna con las técnicas intracutánea (Mantoux—con la dosis apropiada de tuberculina) y transcutánea (Corper).

2. Al presentar una interpretación del significado de los reactores y la relación que guardan con la anespecificidad, señalase lo erróneo que sería justipreciar las pruebas con tuberculina a base del elevado número de reactores. En las encuestas, la prueba mejor es la que descubre el mínimo de reactores entre las personas sin afección tuberculosa.

3. A fin de que las obras de comprobación con tuberculina resulten aceptables, recomiéndase una serie de patrones basados en la eficacia así como en la fidedignidad.

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# SARCOIDOSIS<sup>1</sup>

## A Report of Five Cases with One Autopsy

GERALD F. HOGAN<sup>2</sup>

In the past few years there has been an increased interest in sarcoidosis. The intent of this paper is to present a group of 5 case reports of patients who have had such a diagnosis made at the Philadelphia General Hospital. This group represents all that were so diagnosed in the eight-year period from 1936-1944.

*Case 1:* #68037 M. M., a 27 year old Negress, was admitted to the hospital on October 21, 1939 with the chief complaint of weakness. She was well till nine months before admission when she noted undue fatigue, weakness, exertional dyspnea and mild cough productive of scant, nonbloody sputum. These symptoms continued for six months during which time she lost 35 lbs. in weight. Three months before admission she began to have night-sweats and noted eye fatigue with occasional dull pain in both eyes. One month prior to admission she complained of a dull aching pain in the lower left abdomen which was increased on deep inspiration but which had subsided on admission.

Anamnesis revealed frequent palpitation; nocturia once nightly; and, since the onset of the present illness, marked fluctuation in the amount of her menstrual flow, although no periods were missed. Six years before admission she had pneumonia, three years before admission she had pleurisy and one year before admission she had "painless mumps."

Examination revealed evidence of considerable weight loss; a papular eruption extending around the mouth, *alae nasi* and to a lesser degree about the eyes; limitation of motion of the left chest; tender enlargement of the liver to below the iliac crest; enlargement of the spleen to the iliac crest; generalized, though moderate, lymphadenopathy.

A chest X-ray film taken four months before admission revealed bilateral enlarged hilar lymph nodes and healed minimal apical tuberculous. Another film taken on admission showed similar changes. An X-ray film of the abdomen confirmed enlargement of the liver and spleen, and one of the bones of the hands and feet showed no abnormalities.

Laboratory studies revealed red blood cell counts ranging around three million and white cell counts around 5,000 with 60 per cent polymorphonuclear cells, 30 per cent lymphocytes and 10 per cent monocytes. A Wassermann test was negative. Urine showed a persistently low specific gravity of 1.010. A platelet count was 580,000. The blood protein determinations were as follows: total 7.1, albumen 4.5, globulin 2.6 g. per cent. The A/G ratio was 1.7. Repeated sputa were negative for tubercle bacilli. (In this and the following case reports the sputum reports represent a study of a stained smear of the concentrate of a twenty-four-hour specimen—antiformin method. Cultures of sputum and of gastric juices were not done, except when so stated.) A tuberculin test with .000,02 mg. of PPD was negative, one with .005 mg. was two-plus and a third with 0.1 mg. of Old Tuberculin was two-plus.

Biopsy of the skin lesions showed that the corium was the seat of a fairly dense infiltration of cells of the chronic inflammatory type, together with poorly circumscribed

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collections of mononuclear cells of the epithelioid type. Many of the cellular aggregations show one or more giant cells of the Langhans' type at their periphery. A tentative diagnosis of Boeck's sarcoidosis was made.

A lymph node biopsy was then done and it confirmed the diagnosis. In this specimen the cortex and medulla were both replaced by densely crowded cords and nests of epithelioid cells which showed irregularly shaped nuclei and abundant eosin-staining cytoplasm. Necrosis was absent, although there were a good many giant cells of the Langhans' type, some of which contained calcified inclusions.

The patient's course in the hospital, where she remained for two months, was afebrile and almost asymptomatic. Hence she was discharged to the chest clinic. She failed to return and has since been out of contact with the hospital.

*Comment:* This patient had most of the typical findings of sarcoidosis: painless parotitis early in the course, skin lesions, lymphadenopathy, hepato-splenomegaly, absence of tubercle bacilli, weakly positive skin reaction to tuberculin and typical histological picture in the skin and lymph node biopsies. Chest X-ray films did not reveal pulmonary lesions, except for a healed apical tuberculosis, which may well have accounted for the positive tuberculin tests. Nor did she have any of the bone changes which are usually found in those cases that have such wide-spread involvement as this patient had and especially in those that have skin lesions.

While it is common for patients with sarcoidosis to show no parotid involvement—this syndrome appeared in only 10 per cent of the recent series of 35 reported by Reisner (1) and in none of the 31 reported by Longcope (2)—yet it seems not at all uncommon for those with parotitis to show ultimately wide-spread typical sarcoid lesions. Good accounts of the relative frequency with which various organs are involved in the disease process are presented by Reisner (1), Pinner (3), Longcope (2) Rubin and Pinner (4) and Harrell (5).

*Case 2:* #49025 J. L. was a 36 year old Negro laborer, admitted on January 11, 1940. He was in good health till one year before admission when he noted cough, mild shortness of breath and beginning weight loss. These symptoms had persisted with gradual increase till admission. During this period he had expectorated slight amounts of greenish sputum, but two months before admission it had become blood-streaked. He had lost 15 lbs. in one year. During this time he also occasionally had a "sore feeling" in his chest and occasional night-sweats.

The past history, social history and family history were noncontributory.

The abnormalities found on physical examination were: decreased expansion of the chest with evidence of dense infiltration of both upper lobes, more marked on the right side; enlargement of supraclavicular, epitrochlear and axillary lymph nodes. The admission diagnosis was bilateral pulmonary tuberculosis.

An admission X-ray film revealed mottling throughout the entire right lung and a greater portion of the left upper lobe; slight displacement of the distal end of the trachea to the right and possible cavity at the seventh dorsal interspace on the right side. Repeat films one and fifteen days later showed no changes in the process (figure 1). An electrocardiogram and orthodiagram were normal. Bronchoscopy revealed nothing abnormal but for injection of the mucous membrane of the left main stem bronchus. Six sputum specimens were negative for tubercle bacilli, fungi and molds. Tuberculin

tests with .000,02 mg. and with .005 mg. of PPD were negative. Culture of the sputum detected no tubercle bacilli and material inoculated into a guinea pig produced no disease. X-ray films of the long bones and feet were negative, but those of the hands showed small areas of demineralization of the thumb and middle finger of one hand and of the ring finger metacarpal of the other—circular defects with indefinite borders and considerable alteration of the trabeculation.



FIG. 1

FIG. 2

FIG. 1. (Left) Case 2. Roentgenogram taken shortly after admission to the hospital showing the diffuse mottling throughout the entire right lung and most of the left upper lobe. There is a probable cavity at the level of the seventh dorsal rib on the right and there is slight displacement of the lower end of the trachea to the right.

FIG. 2. (Right) Case 2. Roentgenogram taken two years after that shown in figure 1. There is evidence of progression of the disease process in both lungs with the development of huge, bilateral, multilocular, upper lobe cavities. The patient died within a month of the time this film was made.

A biopsy of a lymph node was performed revealing a typical microscopic picture of Boeck's sarcoid. The normal architecture of the node had been mostly destroyed and the lymphoid tissue replaced by small collections of monocytes and epithelioid cells, in a few of which collections were found Langhans' giant cells.

Caseation and inflammatory reaction were notably absent. Efforts to find tubercle bacilli by appropriate stains were fruitless. However, some densely staining, large, pleomorphic, spheroid bodies were found, the nature of which remained unknown.

Three weeks later an effort was made to confirm this diagnosis, and axillary nodes were removed for biopsy. A very similar microscopic appearance was observed. The previously noted spheroid bodies were not present and giant cells were not seen. Maternal

from these nodes was cultured for tubercle bacilli with negative results and some was injected into a guinea pig but produced no disease.

The patient's course in the hospital was satisfactory with only an occasional low-grade fever, mild cough and expectoration. He was discharged to the chest clinic of the Pennsylvania Hospital, and there he was followed for two years. During this period he made four visits to the clinic, each time complaining of night-sweats, cough and expectoration, and on each occasion sputum tests were negative for tubercle bacilli; yet X-ray films of the lungs showed progression of the lesions with definite cavity formation (figure 2). He was finally admitted to that hospital because of progressive dyspnea, swelling of the abdomen and weight loss. Further search for the tubercle bacillus was fruitless. While studies were in progress he was found dead in bed, approximately three years after the onset of his first symptoms.

At autopsy the lungs appeared relatively normal in size but were covered by dense adhesions, so dense that the upper portions could be separated only by sharp dissection. Enlarged nodes were found in all parts of the mediastinum though no obstruction had been created. The trachea and bronchi were acutely inflamed.

Both upper lobes were found to contain huge multiloculated cavities which occupied almost the whole volume of these lobes. Necrosis was not noted. The remainder of the tissue of both lungs was boggy and very nearly solid, though no obvious pneumonia was found. Fibrous tissue was present in an intense degree.

Microscopic examination showed that in the region of the cavities the lung tissue had been replaced by dense fibrous tissue which extended through the lung to the pleural surfaces. Scattered in this fibrous tissue were cellular aggregates which consisted of lymphocytes, plasma cells, reticulo-endothelial cells and many giant cells. No true tubercles were recognized. In portions of the lung that bordered on the fibrosed area there was also serious damage to the normal structure. Noteworthy in the affected areas were the arteries, all of which showed pronounced intimal thickening while the muscle layers were spared. The veins were normal. The cavities were lined only with fibrous tissue.

The portions of the lower lobes which were examined microscopically revealed congestion with edema and scattered regions of fibrosis similar to that found in the upper lobes. Caseation was absent and giant cells were numerous. A few small abscesses and hemorrhages were found.

All of the lymph nodes showed dense fibrosis which replaced as much as 95 per cent of the normal tissue of some nodes.

The spleen was slightly enlarged and contained innumerable small gray nodules which, microscopically, consisted of small collections of fibrous tissue with occasional giant cells.

The bone marrow again disclosed small agglomeration of dense fibrous tissue containing scattered giant cells. There was no evidence of caseation.

Material from the spleen and lungs obtained at postmortem was injected into guinea pigs and cultures and smears were prepared. No disease was produced in any of the animals; no tubercle bacilli grew on suitable media and smears were negative.

To recapitulate, the unusual features of the autopsy were the lack of evidence of caseation, gross or microscopic, throughout a number of lymph nodes; the dense pleural adhesions; the intense degree of fibrosis in the upper lobes; the cavities involving most of the upper lobes and separated from each other only by shreds of fibrous tissue; the large number of giant cells in many areas not associated with characteristic epithelioid cells and not associated with caseation; the similar changes in the associated lymph nodes; the inability to find acid-fast bacilli despite careful tissue studies with appropriate stains;



the changes in the spleen which was enlarged and contained a number of whorls of hyaline fibrous tissue, giant cells and no evidence of caseation or epithelioid cell formation; the complete absence of these changes in the other organs.

*Comment:* This patient had the disease in one of its common forms: visceral lesions that were almost entirely confined to the lungs and with symptoms referable to the respiratory system. As is common also, this patient had negative tuberculin tests and at no time were tubercle bacilli found despite more than complete search for them. Cases like this one form the main obstacle to the acceptance of the thesis that Boeck's sarcoidosis is a form of tuberculosis. The patient presented, however, a very unusual feature, namely multiple pulmonary cavitation, apparently not produced by caseation. This finding of noncaseating cavitory pulmonary lesions has been reported at least twice before, once by Tice and Sweany (6) and by King (7). The peculiar bodies which resemble yeast more than any common type of living organism likewise have been previously described by several observers but none was able to come to any definite conclusion as to their etiological rôle, if any. Schaumann (8) described yeast-like calcified inclusion bodies which he felt represented a possible etiological agent. Mylius and Schürmann (9), Berg (10), Kraus (11), and Rubin and Pinner (4) have all commented on these structures. Recently, Friedman (12) made a fairly thorough study of these inclusion bodies by histochemical methods but he failed to determine their causation or histological identity.

*Case 8:* #14654 L. T. was a 6 year old Negress who was under observation at the hospital for fourteen months from April 24, 1939 to June 24, 1940. She was brought to the hospital because of painless swelling of the eyelids for the previous three weeks. The swelling was constantly present though more marked in the morning on arising. Examination on admission revealed an asthenic undernourished child who had bilateral painless, nontender swelling of the lacrimal and parotid glands, hepato-splenomegaly, and more or less generalized lymphadenopathy. A diagnosis of Mikulicz disease was made.

Shortly after admission, X-ray films of the chest showed enlarged dense right hilum and increased right lower trunk shadows. X-ray films of the bones of both upper and lower extremities, hips and pelvis were all normal. A white cell count was 5400 with 48 per cent polymorphonuclear cells and 44 per cent lymphocytes. A total protein determination was 8.0 with albumen 4.0 and globulin 4.0 g. per cent, making an A/G ratio of 1.0. Biopsy of a cervical lymph node was diagnosed as acute hyperplasia. Tuberculin test with .000,02 mg. of PPD was negative.

The patient had a slight fever on admission which gradually subsided. Two weeks later she developed an acute upper respiratory infection which improved on symptomatic treatment. About one month after admission it was decided to treat the swollen parotid glands and the cervical lymph nodes with radiation. She received three treatments at weekly intervals consisting of 75 r each. A few days later she developed a severe, typical attack of acute glomerulonephritis with hematuria, hypertension, retention of fluid, oliguria, red cells, white cells and casts in the urine, elevated blood urea nitrogen and elevated sedimentation rates. She gradually recovered from the acute episode, but during the rest of her hospital stay she persistently showed albuminuria, casts, low urinary specific gravity, mild hypertension and poor kidney function tests. Two months after this epi-

sode, pyelograms revealed enlarged kidneys with fair function. Because of the obscurity of the original disease, further studies were then undertaken.

Further tuberculin tests with 0.0025 mg. and with 0.005 mg. of PPD were negative. In another biopsy, this time of a popliteal lymph node, it was found that the lymphoid tissue was almost completely replaced by densely crowded gyriform cords and nests of epithelioid cells showing mostly elongated nuclei and abundant eosin-staining cytoplasm. There were neither caseation nor giant cells. There was no fibrosis. Acid-fast bacilli were not identified. A diagnosis of Boeck's sarcoidosis was made.

A chest film five months after admission disclosed no change in the right hilum but now a large node was present in the left hilum measuring 2.5 cm. in diameter. The child's physical condition grew worse. About six months after admission dyspnea made its appearance and rapidly advanced so that within ten days an emergency bronchoscopy was performed. This demonstrated an obstruction at the larynx, apparently due to encroachment on the lumen by hyperplasia of the surrounding tissues, and also stenosis of the right main stem bronchus from extrinsic pressure. A tracheotomy was done at once. After three weeks, breathing was sufficiently improved to allow removal of the cannula. Eight days later, however, obstruction recurred and a second tracheotomy had to be done. A sternal biopsy ten months after admission was normal. Gradually, within the next four months her respiratory function improved and the tube was successfully removed. She was discharged to the clinic but the family moved out of the state and contact was lost.

*Comment:* Two unusual features of this case are the age of the patient and the complication of respiratory obstruction. The youngest patient in Longcope's (2) series was 10 years old. According to Leitner (13) the disease has been reported in a child as young as three weeks of age. Naumann (14) reported a patient of three months on whom an autopsy was performed. This baby also had laryngeal stenosis and died an asphyxial death from obstruction. Laryngeal obstruction in sarcoidosis, however, is not confined to children, for Spencer and Warren (15) found it in their patient who was 51 years old.

This child presented the typical findings of Mikulicz's syndrome, hilar enlargements, adenopathy, hepato-splenomegaly, negative tuberculin tests and a tendency toward reversal of the A/G ratio. Hyperproteinemia, hyperglobulinemia and reversal of the A/G ratio are laboratory findings that were commented on even in the early reports of sarcoidosis. In the group presented by Longcope (2), 19 patients had protein determinations; 13 of these were over 7.0 per cent, and of these, 5 were between 8.0 and 9.0 per cent. All of the 19 had globulin determinations above the standard normal of 2.58 per cent. In Reisner's (1) series, 22 patients were tested and 8 showed a total of more than 7.0 and 6 of these more than 7.5 per cent. Furthermore, a tendency toward reversal of the A/G ratio was present in several of those patients who had normal total protein content.

*Case 4:* #77326 I. F. was a 21 year old Negress who first came under observation in 1933 at the age of 14. At that time she had extreme fatigue and evident malnourishment. A tuberculin test was negative and the chest X-ray film was normal. However, she was found to have marked hepato-splenomegaly, anemia and a basal metabolic rate of plus 21. She was seen occasionally during 1934 and 1935. During this time dyspnea and cough had become prominent symptoms. Fine râles were heard in the left base. The liver and

spleen remained enlarged. She returned to the clinic in 1940, still complaining of cough and shortness of breath. Numerous fine râles were heard over both lungfields. The sedimentation rate was normal; the tuberculin test was three plus to .005 mg. of PPD. Sputum was negative for tubercle bacilli; the blood counts were normal; a chest X-ray film was reported as showing miliary tuberculosis and so the patient was referred to the hospital.

On admission she added to the history the points that she had lately been losing weight, that cough had increased and that she had occasional mild chest pain on the left side, but especially that she had become quite weak. Her father had died of tuberculosis. Physical examination revealed evidence of malnutrition, diffuse enlargement of the thyroid gland, evidence of infiltration of the lungs, hepato-splenomegaly and generalized mild lymphadenopathy.

X-ray films were reviewed and opinion was divided as to etiology but the process was not typical of miliary tuberculosis. The blood counts were normal. The total protein was 6.9 with albumen 3.7 and globulin 3.2 g. per cent. The A/G ratio was 1.2. Repeated sputa were negative for tubercle bacilli. A sternal marrow biopsy was reported as showing tuberculosis of the bone marrow.

She remained in the hospital for about a month, during which time she regained her strength, had normal temperature, pulse and respiration, and a good appetite. She became restless in the hospital and signed out against advice.

*Second admission:* Two and a half months after her discharge she was readmitted in a thyroid crisis with a temperature of 103° F. She had had three convulsions just prior to admission. She recovered from this storm, but ten days later the basal rate was still plus 54. At this time the first positive sputum was obtained. The basal metabolic rate gradually declined to plus 22 and the patient felt much improved. She continued to have tubercle bacilli in her sputum although her temperature, pulse and respiration were normal. She gained eight pounds in four months.

A bronchoscopy disclosed no abnormalities. A chest film at this admission revealed considerable dense mottling throughout the entire right lung and also in the left lung. However, the appearance did not suggest miliary tuberculosis. Repeated X-ray films at suitable intervals revealed no change. X-ray films of the skull, stomach, spine, pelvis were all normal. An electrocardiogram and orthodiagram were normal. A chest film taken after the patient had been in the hospital four months on the second admission showed still no change in the pulmonary lesions. Eye grounds and visual fields were normal. Despite the ominous diagnosis of miliary tuberculosis, she continued to improve clinically, so much so that she was well enough to sign out of the hospital against advice. She was referred, however, to the Phipps clinic but failed to return and contact has been lost.

A review of the sternal biopsy was done and it was found that the bone marrow showed several circumscribed, partially confluent nodules of epithelioid cells with mostly elongated nuclei and a good many giant cells of the Langhans type, some of which contained star-like inclusions. There was no necrosis present. The blood forming tissue of the marrow appeared to be essentially normal. There were a good many eosinophilic leucocytes in both the granulomata and the normal bone marrow tissue. A diagnosis of Boeck's sarcoidosis was made.

*Comment:* This patient is an example of a situation that happens not rarely in sarcoidosis—a diagnosis of miliary tuberculosis is made; and, because of the quiescent clinical course of certain cases of chronic miliary tuberculosis, the dis-

tion is not possible except by biopsy. It may be proposed, however, that these cases are in reality sarcoidosis. Certainly this could be maintained in those cases of chronic miliary tuberculosis in which the diagnosis is made almost solely on X-ray evidence. Hoyle and Vaizey (16) have published a monograph reporting 120 cases of chronic miliary tuberculosis. Yet in a fairly large proportion of such cases the diagnosis is not rigidly established, even at autopsy. Weleh (17) reported a case and in his discussion comments on the possibility of some of these cases being sarcoidosis.

This patient had hyperthyroidism and a tuberculous infection of the lung. There is no valid reason, however, for accepting the whole picture as tuberculosis, as is sometimes done. Outstanding, too, was the marked hepato-splenomegaly which was found very early in the course of the disease. Splenomegaly is somewhat more common than hepatomegaly. In 6 patients who were autopsied, Niekerson (18) found splenic enlargement in 5. Among Reisner's (1) 35 patients there was clinically demonstrated enlargement of the spleen in 8.

*Case 5: #119427* This patient was a 27 year old Negress who was admitted from another hospital on September 21, 1942. Her chief complaints were shortness of breath and pain in the right upper abdomen. Two years prior to admission she had attended a New York hospital because of bilateral swellings of the parotid glands. After various studies there, a diagnosis of sarcoidosis was made, although unconfirmed by microscopical evidence. One month prior to admission here, she was admitted to another Philadelphia hospital where it was learned that she had had episodes of chills, fever, sore throat, conjunctivitis and rhinitis since 1929; that she had a period of amenorrhea from January, 1941 to August, 1942. A physical examination at that time revealed a slightly productive cough; mild adenopathy; discrete, red-black petechial skin lesions; a granulomatous type of chronic conjunctivitis; firm, nontender bilateral parotid swelling with inflammation of Stenson's ducts; nasal injection and discharge; moist râles in both lungs; orthopnea and mild dyspnea; generalized abdominal tenderness, especially in the upper quadrants; and hepatomegaly.

Laboratory studies showed a blood protein level of 8.6 with albumen 3.6 and globulin 5.0 g. per cent. The A/G ratio was .75. A Wassermann test was negative. An X-ray film of the lungs disclosed bilateral mottling but no evidence of cavity. X-ray films of the bones of the hands were normal, while those of the abdomen demonstrated gallstones. A tuberculin test with 0.1 mg. of OT was negative. A biopsy of a supraclavicular lymph node revealed a typical picture of Boeck's sarcoid.

She was kept on the ward and sputa were examined repeatedly for tubercle bacilli. After 5 negative, 4 more successive specimens were positive and hence the patient was transferred to the Philadelphia General Hospital.

On admission here, the findings were all essentially as above. The blood protein was 9.2 total and albumen 2.7 with globulin 6.5 g. per cent, giving an A/G ratio of 0.41. Sputum was positive for tubercle bacilli. All the bones of the hands and feet were found to be normal on X-ray examination. The previously found discrete mottled shadows in both lung fields were still present without much change and the films were interpreted as miliary tuberculosis. There was more marked fibrosis in the region of the left apex and no evidence of cavitation.

Her physical condition remained stationary for about a month and then she signed out of the hospital against advice. She was traced back to another New York hospital where

she was admitted with far advanced, bilateral cavitary tuberculosis of the lungs and with positive sputum. She went rapidly downhill and died of pulmonary tuberculosis. An autopsy was not performed.

*Comment:* This patient is an example of a not uncommon outcome—death from rapidly advancing tuberculosis. This fact has often been put forth as an argument to support the view that Boeck's sarcoidosis is a benign form of tuberculosis, that is, a noncavitating tuberculosis. In fact, except for the biopsy specimen, it would be difficult to maintain that the disease in this patient was not tuberculosis from the beginning. As frequently happens also, X-ray films were interpreted as miliary tuberculosis on several occasions, despite the total lack of confirmation as judged by the patient's clinical status and course. That the tuberculosis was superimposed could be supported by the negative tuberculin test and the failure to find tubercle bacilli at first and the later development of a positive sputum and the beginning of a rapid decline to death. Unfortunately, a tuberculin test was not done following the appearance of a positive sputum. If positive, then such a test would have delineated very well the onset of the tuberculosis process.

This patient showed also the marked changes that occur in the blood proteins in some cases of sarcoidosis. She also had previously had Mikulicz's disease and some skin lesions, but from the record it is difficult to evaluate these lesions since no biopsy was done of the skin.

#### DISCUSSION

The problem of etiology always arises whenever the subject of sarcoidosis is discussed. Is this a distinct disease entity or is it a form of tuberculosis, a benign form which can change under certain undefined circumstances into the typical tuberculosis with which we are familiar?

The answer to this question can be determined neither by reading the literature nor by studying case reports. There is a large group of cases, many with autopsies, in which there has never been found any evidence of tuberculosis despite rigorous search. It is difficult to lay these cases at the door of "benign tuberculosis" or even "atypical tuberculosis," for nothing substantiates the inclusion of tuberculosis in the diagnosis. Such a case is the second one of the group here presented. On the other hand, there is a group of cases, also with autopsy reports, where one is led to the conclusion that sarcoidosis developed into typical tuberculosis. Such a case is that reported by Rubin and Pinner (4). Certainly, however, in some of the cases in which transformation of the lesion is reported, it is not possible to completely exclude the possibility that tuberculosis was superimposed on the sarcoid lesions. Even in some of the autopsied cases of typical sarcoidosis there is found an old healed fibrocalcific or fibroid tuberculous lesion that could account for the occasionally positive tuberculin tests. Furthermore, it is possible that a sarcoid lesion could so impinge on a healed tuberculous lesion as to destroy the capsule that keeps the bacilli pent up and thus to allow for the dissemination of tubercle bacilli in the lung itself, or through the blood-stream to other parts of the body. Such a chain of events could well

have taken place in the fifth case in this present group. (Such a chain of events has already been adequately demonstrated to occur in other diseases, that is, reactivation of healed or quiescent tuberculosis due to the superimposition of influenza (19, 20, 21), nontuberculous pneumonia (22, 23, 24, 25, 26, 27), lung abscess, bronchiectasis and purulent lung infections (26)).

In an article published in 1938, Pinner (3) reported on all the autopsies in the literature—a total of 18—and he reviewed the literature. In that paper he set up eight reasons in favor of the tuberculous etiology of sarcoidosis and crystallized the consensus of those holding such an opinion. Since then, Rubin and Pinner (4) have brought the subject up to date by reporting 25 more autopsies making a total of 43 autopsies in the literature. The second patient in the present series has not previously been reported. The following is a restatement (with the writer's comments) of Pinner's eight points.

(1) *The demonstration of tubercle bacilli in sarcoid lesions:* In a thorough search of the literature, Pinner was able to find 25 cases where tubercle bacilli were found in the lesions either by section, culture or animal inoculation and where the occurrence of frank tuberculosis was not also noted. The number of cases reviewed in order to find these 25 positive ones is not stated, although it is stated that "the number of positive results is very small; the number of completely convincing positive results is insignificant."

(2) *Histological characteristics:* By this is meant the similarity of the sarcoid tubercle to the tuberculous tubercle. The differences between these tubercles is not emphasized and the fact that agents other than the tubercle bacillus can cause such a tissue reaction is passed over lightly.

(3) *Transformation of sarcoidosis into classical tuberculosis:* In 3 of the 18 cases (3) death was due to tuberculosis. In 3 more tuberculosis was found to be present though not the cause of death. This makes an incidence in this group of 33 per cent. It was the opinion of the pathologists who did the autopsies that the gross and microscopic examinations revealed evidence of transformation of one lesion into another. While this is offered as an argument in favor of tuberculous etiology, actually this is the statement which is to be proved.

(4) *Anergy or the failure of patients with sarcoidosis to react to tuberculin:* While this is usually adduced as a reason for the reverse view, Pinner holds that the anergy is so frequent as to be more than coincidental and therefore due specifically to a deterring effect of the sarcoid lesions. But just why the latter, even though true, should be held as an indication of the tuberculous etiology is not entirely clear. He culled from the literature, mostly German, 3 large series of 82, 46 and 100 patients with negative tuberculin reactions in 73, 62 and 72 per cent, respectively. Harrell (5) found 66 per cent of those tested were tuberculin-negative. Longcope (2) found anergy in 85 per cent; Kissmeyer (28) in 60 per cent; Martenstein (29) in 70 per cent and Reisner (1) in 60 per cent of patients tested.

(5) *Disappearance of sarcoid lesions with the development of frank tuberculosis:* It has been observed by Ronchese (30), by Thomas (31) and by Schaumann (32) that in certain cases of sarcoidosis the lesions of the skin have disappeared with the development of positive tuberculin reactions, positive sputa and advancing

lesions in the lungs. It has also been observed (3) that the lesions will regress in one organ and progress in another. The conclusion is thus reached that sarcoidosis changes into frank tuberculosis and that sarcoidosis is a phase of tuberculosis which passes out of existence as the next phase appears. Regression, however, is a characteristic feature of sarcoidosis even without the occurrence of frank tuberculosis. Thus, Reisner (1) noted spontaneous regression in 7, or 50 per cent, of 14 patients who had cutaneous lesions, and regression in various organs was an outstanding feature in one-third of his whole group.

(6) *Serological data, anticutins and procutins:* Substances have been found in the sera of sarcoidosis patients which are capable of either preventing the production of a typical tuberculin reaction in a known positive reactor, "anticutins," or of enhancing such a reaction, "procutins." Subsequently, Pinner, Weiss and Cohen (33) studied these substances and found them to occur in normal persons and in tuberculous patients in sufficient percentages to make their occurrence in patients with sarcoidosis of no diagnostic, etiological or pathognomonic significance. Pinner further studied some of the cases reported by Reisner (1) and no definite conclusions could be drawn. It has been mentioned that many patients with sarcoidosis have hyperproteinemia and globulinemia and a tendency to reversal of the A/G ratio. One may speculate on the rôle of this altered protein metabolism as the explanation for the appearance of anticutins and procutins.

(7) *The simultaneous or successive occurrence of lesions definitely or probably tuberculous:* Pinner reports (3) that "some form of tuberculosis, coexisting with sarcoid, preceding, or following it, is reported in approximately 10 per cent of the cases." The importance of this comment is that it was found in *only* 10 per cent.

(8) *The close similarity between sarcoid reactions in humans and in certain animal species:* Here, reference is made to the fact that rats react to infection with tubercle bacilli with a lesion that looks and acts like that found in human sarcoidosis (34). There is no caseation, no reaction to tuberculin and there are anticutins in their blood sera. While nothing is mentioned about it, one is led to assume that in animals the tubercle bacillus can be found within the sarcoid-like lesion, a situation which is distinctly different from that in human sarcoidosis where organisms are rarely found.

And so it would appear that, though there is something to say about each of the eight arguments in favor of the so-called tuberculous etiology of sarcoidosis as presented by Pinner, many of these arguments may and have been used by the proponents of the nontuberculous etiology of sarcoidosis. The greatest obstacle to the acceptance of the tuberculous etiology is the easy possibility of tuberculosis being superimposed on the sarcoid process. Longcope (2) has stressed the frequency with which patients with sarcoid develop superimposed infections like bronchopneumonia. Tuberculosis might well be included.

In the overwhelming majority of sarcoid patients it is impossible to hold to tuberculosis as the whole disease or any part of it. This is true in the larger portion of autopsies. Hence in the total of 44 autopsies in the literature (including the one presented in this series) the presence of active tuberculosis or of tubercle

bacilli was detected in 11, or 25 per cent, of the cases, and in only 5, or 11 per cent, was tuberculosis the cause of death. Certainly if the tubercle bacillus were the etiological agent it is not conceivable that it could remain undetected in cases such as the second of this series where there was wide-spread destruction of tissue and where a more than adequate search with multiple methods proved fruitless.

Harrell (5) has undertaken an extensive investigation into the etiology of sarcoidosis through the study of 11 patients with sarcoidosis. He could reach no conclusion.

This question of etiology will be suitably settled only when a sufficiently large series of sufficiently well studied cases with autopsy reports is on record. Early diagnosis, adequate histological and bacteriological study, continuous and complete follow-up and postmortem examinations where death supervenes will form the foundations in fact for the more definite delineation of sarcoidosis either as a specific and individual disease entity or as a phase of human tuberculosis.

#### SUMMARY

Four cases of sarcoidosis proved by biopsy and one additional case proved by autopsy are reported in detail. Brief comments are made on each. The question of etiology is discussed and the main points that support the thesis that sarcoidosis is a form of tuberculosis are restated. Each of these points is discussed from the point of view that sarcoidosis is not a form of tuberculosis, this latter opinion being that of the author.

#### SUMARIO

Contiene este trabajo una reseña minuciosa de cuatro casos de sarcoidosis comprobados por la biopsia y uno más comprobado en la autopsia, con breves comentarios acerca de cada uno de ellos. Discútese el problema etiológico y los principales puntos que apoyan la tesis de que la sarcoidosis constituye una forma de tuberculosis, analizándose cada uno de estos argumentos desde el punto de vista del A., de que la sarcoidosis no es una forma de tuberculosis.

#### Acknowledgments

I am indebted to Dr. David Cooper of Philadelphia for his permission to report the second case in this group; and to Dr. W. E. Ehrlich, Department of Pathology of the Philadelphia General Hospital, and Drs. R. F. Norris and J. T. Bauer, Department of Pathology of the Pennsylvania Hospital, for their interpretations of biopsy and autopsy findings.

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# RETARDANTS TO THE GROWTH OF TUBERCLE BACILLI<sup>1,2</sup>

## The Effect of Caramelization on Growth

H. J. CORPER AND C. CLARK

In growing tubercle bacilli for diagnostic purposes, it is particularly pertinent that there be no retarding influences, either generally present in a good nutrient medium or distributed in local spots throughout the medium or on its surface.

In a rather general way, attention was called to this matter in a number of previous communications in which it was pointed out that drying of a good nutrient medium (1) could lead to erroneous deductions concerning its nutrient qualities or to the retarding effect of certain added ingredients upon the growth of the bacilli. It was also noted earlier that paraffin or paraffin oils in a thin film on the surface of the medium could retard growth, partially or completely, on good, solid, otherwise adequate, nutrient media, as well as on relatively poor nutrient liquid media (2) (from the standpoint of supporting growth from small plants). Thus it was indicated also that the addition of antiseptic or bacteriostatic substances such as the dyes (gentian violet, malachite green) and other retardants in this category would display definite inhibitory effects (3) upon growth of small plantings, although apparently not perceptibly affecting heavy plantings on good nutrient media. It became evident from these studies that ordinarily considered inconsequential variations in media would be particularly important in assuring positive or maximum growth, especially of the slow growing mammalian tubercle bacilli which might not be significant otherwise. Such considerations also became pertinent within recent years with the advent of numerous new antibiotics. Claims for activity of these antibiotics were based mainly upon the retardation of the growth of tubercle bacilli on a relatively poor nutrient medium, such as glycerol broth, Long's nonprotein synthetic asparagin medium or any similar simple synthetic medium.

Pertinent to the local retarding effect in a medium, and particularly emphasized by the greater prevalence of poor grade eggs during periods of war and shortage, were the results noted frequently with all types of egg media. As the eggs became older, because of storage or otherwise, there was a tendency toward the liberation of fatty substances which would either coat the surface of the completed egg media after sterilization (being also more evident the longer the sterilization) or would float on the water of condensation at the bottom of the tube of medium. Such retardation of growth, caused by the fatty materials in the water of condensation, is illustrated in figure 1. This picture shows the absence of growth on a tube of malachite green egg medium received from the Kansas State Tuberculosis Sanatorium. An egg medium prepared from fresh eggs should be as free as possible of this oily surface effect to avoid retardation of growth, and only strictly fresh eggs are advised for the preparation of diagnostic egg media.

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<sup>2</sup> This investigation was aided by a gift from Morton May in memory of Florence G. May.

Another fault in the preparation of nutrient media for tubercle bacilli is well illustrated by the retarding effect noted upon the growth and yield of culture mass on simple synthetic nonprotein media, containing sugar in some form, which have been sterilized to the point of evident partial caramelization. In

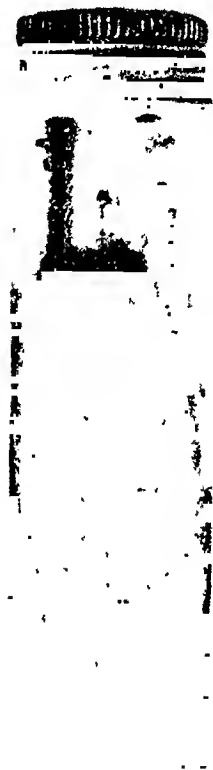


FIG. 1

FIG. 1. The retarding effect of fatty materials in a malachite green egg-potato medium upon the growth of human tubercle bacilli. Note the fat droplets on the surface of the medium at the lower part of the medium slant and the absence of appreciable growth as compared with the luxuriant growth above.



FIG. 2

FIG. 2. The retarding effect of caramelization of glucose upon the growth of human tubercle bacilli on a liquid medium. Note the greater amount of culture mass after three week's incubation at 37°C. on the control bottle at the left as compared with that on the bottle containing the caramelized medium at the right.

illustration, such an experiment was performed using Wong's malic acid non-protein liquid medium containing glucose. One part of the medium was prepared by mixing the ingredients completely and then autoclaving the mixture at 15 lbs. pressure (115°C. in the exhaust line) for one hour; while in the regularly prepared preparation, the medium constituents and glucose were autoclaved (sterilized) separately, the latter being added carefully after sterilization from a concentrated solution (20 per cent). The nonprotein synthetic medium used

for these tests was that previously described by Wong and Weinzirl (4) and consisted of the following constituents: malic acid, 3 g.; ammonium hydroxide 10 per cent solution, 12 cc.; ammonium citrate, 5 g.; monopotassium acid phosphate, 6 g.; sodium carbonate (anhydrous), 2 g.; sodium chloride, 2 g.; magnesium sulphate, 1 g.; ferric ammonium citrate, 0.05 g.; glycerol, 50 cc.; distilled water to make 1,000 cc.; and 10 g. glucose solution (added after sterilization). While the Wong-Weinzirl medium prepared by adding the separately sterilized 20 per cent glucose solution was a clear pale straw color, that in which the glucose was added to the rest of the ingredients before autoclaving, though clear, had a very decided brown tint caused by the caramelization of the glucose. The photograph, figure 2, illustrates the amount of growth obtained on the control nutrient medium (bottle on the left) after three weeks' incubation at incubator temperature (37°C.), while the retarded growth on the caramelized medium at this same time is shown in the bottle on the right. At the one-month incubation period, the tubercle bacilli were separated from the liquid nutrient medium; and they were then dried *in vacuo* at 50°C. to remove all moisture and, after drying, were weighed. The following results illustrate the differences obtained in growth: The yield in dry weight (moisture free) bacilli, obtained from the 500 cc. caramelized medium in liter bottles, was 1.22 g. while the yield from the same amount of regular Wong's nonprotein synthetic glucose medium was 3.29 g., an approximate loss of 2.07 g., or about 61 per cent in yield, as the result of the retardation resulting from caramelization of the glucose by the heat of sterilization.

#### CONCLUSIONS

It was the purpose of this study on the growth of mammalian tubercle bacilli to call attention again to the various important factors inherent in the proper preparation of nutrient media for the diagnostic culture of tubercle bacilli (on good nutrient media) or for the production of optimum bacillary mass (on relatively poor synthetic nutrient media). It cannot be stressed too often that diagnostic egg culture media should be prepared from strictly fresh eggs and should be autoclaved adequately to assure sterility. Overautoclaving encourages the liberation of detrimental fatty materials from the egg which, when present on the surface of the medium, tend to inhibit the growth of the mammalian tubercle bacilli. Old eggs tend to have a greater preponderance of free fatty materials and are less easily sterilized and therefore become unsuited to the preparation of satisfactory diagnostic culture media for growing mammalian tubercle bacilli. Likewise, in growing mammalian tubercle bacilli on liquid synthetic media, it is desirable to prepare these media in such a way as to prevent retarded cultures which result from the presence of inhibitory substances formed either by excessive sterilization or by permitting caramelization of sugars to occur to any appreciable extent. Such caramelization which may result from autoclaving of glucose (sugar) in the mixed media may retard the growth of mammalian tubercle bacilli sufficiently to cause a deficit of about 60 per cent or more of the culture mass following four weeks' incubation at 37°C. Aside from contamination of the medium, which must be avoided rigidly in growing mammalian tubercle bacilli, these detrimental effects in the media themselves are to be

guarded against carefully if successful and speedy development of the bacilli is to be attained. For this reason, constituents naturally contaminated, such as dairy products and milk, are not advised as adjuvants to nutrient media for the purpose of growing mammalian tubercle bacilli for diagnostic or scientific purposes.

#### CONCLUSIONES

El propósito de este estudio sobre el crecimiento del bacilo tuberculoso de los mamíferos, era llamar de nuevo la atención sobre los diferentes factores importantes inherentes a la preparación adecuada de medios nutritivos para el cultivo para diagnóstico del bacilo tuberculoso (en buenos medios nutritivos) o para la producción de masa bacilar óptima (en medios nutritivos sintéticos relativamente pobres). No puede recalarse demasiado que los medios de cultivo de huevo deben prepararse de huevos perfectamente frescos y someterse al autoclave en forma adecuada para asegurar la esterilidad. Un exceso de esterilización al autoclave favorece la liberación del huevo de sustancias grasas perjudiciales, que al hallarse presentes en la superficie del medio, tienden a cohibir el crecimiento de los bacilos tuberculosos del mamífero. Los huevos viejos suelen mostrar preponderancia mayor de materias grasas libres y son más difíciles de esterilizar y por lo tanto, menos adecuados para la preparación de medios de cultivo satisfactorios para el desarrollo de los bacilos tuberculosos de los mamíferos. Igualmente, al cultivar bacilos tuberculosos de mamíferos en medios sintéticos líquidos, conviene preparar dichos medios de tal modo que no se presenten los cultivos tardíos debidos a la presencia de sustancias inhibitorias formadas, bien por excesiva esterilización o por dejar que se acaramelan los azúcares en forma apreciable. El acaramelamiento que puede resultar de someter la glucosa (azúcar) al autoclave en los medios mixtos, puede retardar el crecimiento de los bacilos tuberculosos de mamífero lo suficiente para producir un déficit aproximadamente de 60% o más de la masa de cultivo al cabo de cuatro semanas de incubación a 37°C. Aparte de la contaminación del medio, que debe evitarse rigurosamente al cultivar los bacilos tuberculosos de mamíferos, hay que resguardarse cuidadosamente contra estos efectos perjudiciales en los medios mismos si se va a obtener el rápido desarrollo del bacilo. Por esta razón los componentes naturalmente contaminados, tales como la leche y los lacticinios, no se recomiendan como complementos de los medios nutrientes utilizados para cultivar bacilos tuberculosos de mamífero para fines de diagnóstico o científicos.

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# TUBERCLE ENDOTOXOID (GRASSET) IN EXPERIMENTAL TUBERCULOSIS IN GUINEA PIGS

WILLIAM H. FELDMAN<sup>1</sup> AND H. CORWIN HINSHAW<sup>2</sup>

The name "tubercle endotoxoid" has been proposed by Grasset (1) to designate an extract prepared from cultures of smooth mammalian strains of *Mycobacterium tuberculosis* by heating the bacterial cells at 60°C. for thirty minutes followed by repeated freezing at -30°C. After centrifugation the product is finally submitted in the presence of a hydrolyzed peptic medium to the detoxicating action of formalin. It is said to contain the water-soluble lipoid fraction of tubercle bacilli, small amounts of bacillary protein and perhaps traces of carbohydrate.

The use of tubercle endotoxoid in the treatment of clinical tuberculosis has been reported by Grasset (1, 2). In a report published in 1939 Grasset concluded that, on the basis of clinical, radiological and bacteriological criteria obtained by a study of 242 cases, "endotoxoid exerts a definite therapeutic action in tuberculous patients." In another report published in 1944 (2) on the results obtained with endotoxoid in treating South African Bantu natives, further evidence of therapeutic effect of tubercle endotoxoid on tuberculosis was presented. In early or moderately advanced tuberculosis, healing of the lesions by fibrosis was reported and there was frequently a reversal of a positive to a negative sputum. In some cases in which the disease was more advanced there appeared to be a transformation of the soft, spreading type of the disease to a chronic fibrocaseous or fibrotic tuberculosis, frequently with disappearance of tubercle bacilli from the sputum.

In view of the reported therapeutic effect of tubercle endotoxoid in many different forms of clinical tuberculosis in man, it seemed important that the substance be tested under controlled laboratory conditions to determine its possible deterrent action on experimental tuberculosis of guinea pigs. Accordingly Dr. Grasset offered to supply the amount of the substance necessary for our experiments.<sup>3</sup>

## METHODS

Sixty-four adult male guinea pigs, having an average weight of approximately 600 g., were each inoculated subcutaneously with 0.001 mg. of a twenty-three day old culture of the virulent variant of human strain tubercle bacilli H37 (H37Rv). The animals were caged in pairs and maintained on a standard laboratory ration. Twenty-four days after the animals had received the infecting dose of tubercle bacilli the 64 animals were divided into four groups, each containing 16 guinea pigs. Group 1 was composed of the untreated controls. In group 2 the animals were to be treated with tubercle endotoxoid only. Group 3

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<sup>3</sup> Dr. Grasset suggested certain modifications of the experimental methods submitted to him for approval and also outlined the dose schedule to be followed.

was to be treated with promin, while the animals in group 4 were to receive promin and tubercle endotoxoid.

*Dosage:* The dose schedule for the animals that received tubercle endotoxoid was that suggested by Dr. Graciet. The material was injected subcutaneously twice weekly (Tuesdays and Fridays) as follows: first week, 0.1 cc. and 0.2 cc.; second week, 0.4 cc. and 0.6 cc.; third week, 0.8 cc. and 1.0 cc.; fourth week and thereafter, 1.0 cc. and 1.0 cc. The dose schedule for promin was 400 mg. given in the feed daily.

Medication of the treated groups was started on the twenty-fourth day after the animals had been inoculated with tubercle bacilli. Treatment was continued for a total of 182 days, at which time the supply of tubercle endotoxoid was exhausted. When treatment was stopped the experiment was terminated, 206 days after the animals had received their infecting dose of tubercle bacilli.

At the time of necropsy, tissues from the lungs, liver and spleen, the site of injection and the contiguous lymph nodes were preserved for subsequent histopathological study.

## RESULTS

*Mortality:* During the period of infection, which, as mentioned previously, was 206 days, the mortality rate in the respective groups was as follows: group 1, untreated controls, 81.2 per cent; group 2, treated with tubercle endotoxoid only,

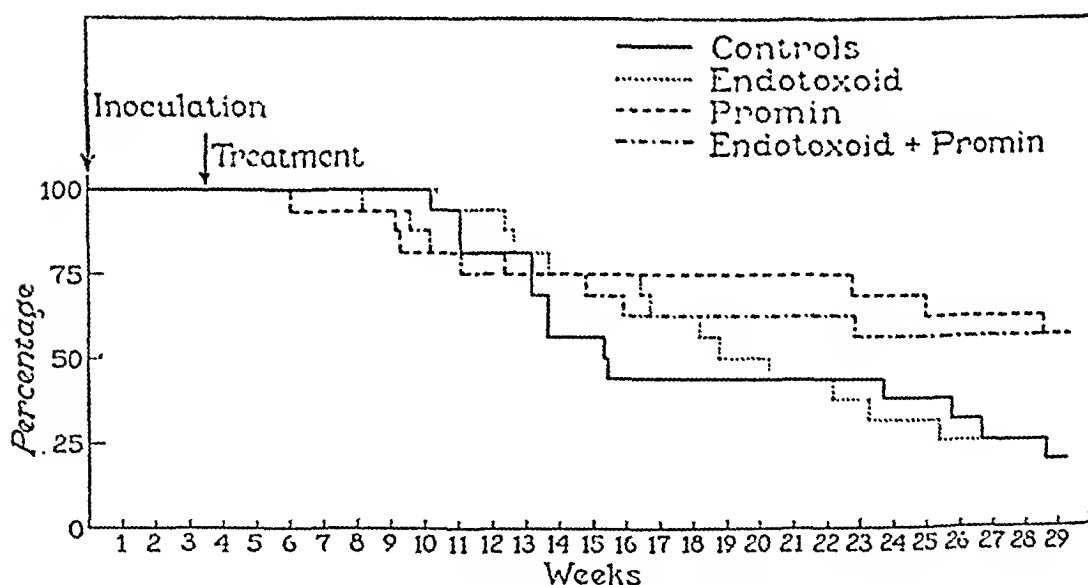


Fig. 1. Survival curves of the respective groups of infected guinea pigs

81.2 per cent; group 3, treated with promin only, 43.8 per cent; group 4, treated with promin and tubercle endotoxoid, 43.8 per cent. The survival curves for the respective groups are shown in figure 1.

*Findings at necropsy:* At the time of necropsy the grossly visible lesions of

tuberculosis were recorded schematically. These observations are recorded diagrammatically in figures 2 and 3, according to the method previously described (3).

*Morphological evidence of effects of treatment:* The tissues collected at the time of necropsy were examined microscopically and the relative amounts of tuberculosis and the character of the lesions were determined. The results were expressed

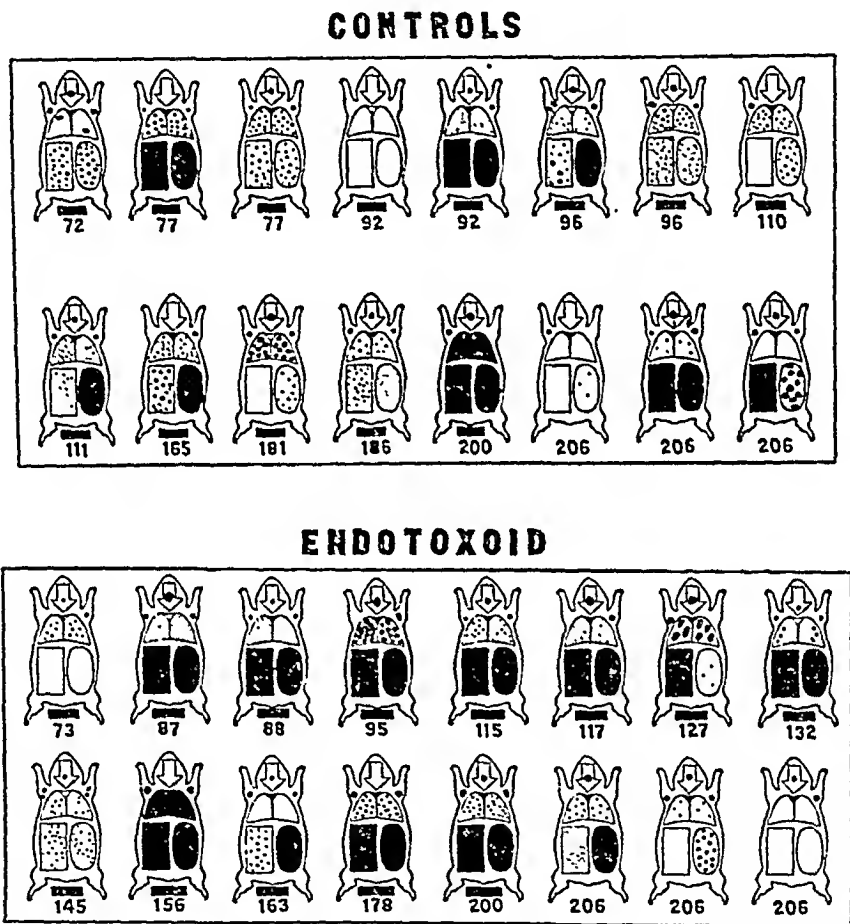


FIG. 2. The amount and distribution of tuberculosis recorded diagrammatically at the time of necropsy in the group of untreated controls and in the group of animals treated with tubercle endotoxoid. (A black bar indicates that a particular animal died and the respective numerals indicate the number of days of infection.)

numerically according to a scheme described previously (4). A summary of this phase of the study is shown in table 1.

The experimental data may be summarized briefly as follows: The highest mortality occurred in the untreated group and in the group that had been treated with tubercle endotoxoid alone. In each of these groups all but 3 of the original 16 animals had died. The rate of survival in the other two groups was also identical; 9 animals in each of these groups were living when the experiment



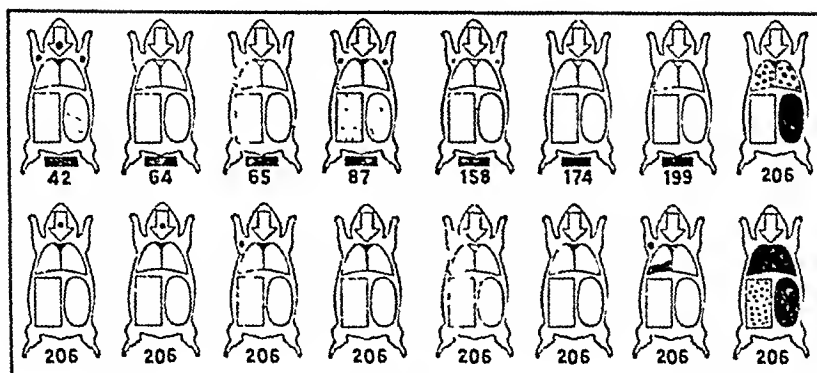
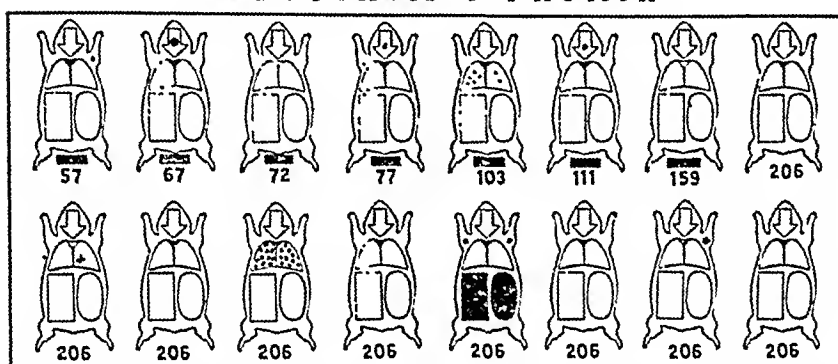
**PROMIN****ENDOTOXOID + PROMIN**

FIG. 3. The amount and distribution of tuberculosis recorded diagrammatically at the time of necropsy in the group of animals treated with promin and in the group treated with endotoxoid plus promin. (See figure 2 for explanation of symbols.)

TABLE 1

*Average severity of tuberculosis in different anatomic situations expressed numerically; data based on histopathological examination of tissues*

GROUP*	SPLEEN (MAXIMUM 35)	LUNGS (MAXIMUM 30)	LIVER (MAXIMUM 25)	SITE OF IN- OCULATION (MAXIMUM 10)	AVERAGE INDEX OF INFECTION (MAXIMUM 100)
Controls.....	27.2	18.4	19.3	9.3	74.2
Tubercle endotoxoid only.....	31.1	24.0	20.2	10.0	85.3
Promin only.....	6.3	6.3	3.1	2.0	17.7
Tubercle endotoxoid plus promin.....	2.37	2.0	1.87	1.37	7.61

\* Each group contained 16 guinea pigs.

was terminated. Quantitatively and qualitatively the most severe tuberculosis occurred in the animals of the group that was treated with tubercle endotoxoid only. While grossly there appeared to be little difference between the amount

and character of the tuberculosis in the group that was treated with promin only and the group that received promin and tubercle endotoxoid (figure 3), microscopically there was evidence of a greater deterrent effect in the latter group than in the former. As shown in table 1, the numerical index of infection among the animals treated with promin was 17.7 as compared to an index of infection of 7.61 for the animals in the group that received both promin and tubercle endotoxoid.<sup>4</sup> The results show definitely that tubercle endotoxoid alone failed to exert any therapeutic or deterrent effect.

#### COMMENT

The results of this experimental study of the effect of tubercle endotoxoid on previously established tuberculosis of guinea pigs failed to yield the result which should be anticipated in view of the favorable clinical results reported by Grasset. The conditions governing the clinical use of tubercle endotoxoid were markedly dissimilar to those that obtained in tuberculosis induced experimentally. The guinea pig has much less natural resistance to human (or bovine) tubercle bacilli than is true with man. Furthermore the pathogenesis of experimental tuberculosis offers many contrasts with tuberculosis of man which is acquired naturally.

Under the conditions of the experiments reported, it was definitely established that the infection which had been induced experimentally was amenable to the favorable influence of promin, although the degree of therapeutic response was lower than in previously reported studies (5). Under the same conditions the infection failed to respond favorably to the administration of tubercle endotoxoid. The apparently increased efficacy of the combined treatment with promin and tubercle endotoxoid can be correlated with the results reported by Steenken, Heise and Wolinsky (6), who noted that promin was more effective when combined with vaccine therapy than when used alone. This result suggests the desirability of further study of the synergistic effects of various fractions of the tubercle bacillus when given in combination with a chemotherapeutic agent to combat tuberculous infections. It is obvious that the data from these experiments are not adequate to provide convincing evidence of the benefits of the combined administration of promin and tubercle endotoxoid.

#### SUMMARY AND CONCLUSIONS

Using tubercle endotoxoid furnished by Grasset, experiments were done to determine the effect of this substance on the course of experimental tuberculosis in guinea pigs. Four groups of 16 guinea pigs each were utilized. All were inoculated subcutaneously with 0.001 mg. of a human strain of tubercle bacilli (H37Rv). One group was untreated and served for controls. One group was treated twice weekly for 182 days with tubercle endotoxoid only; another group received promin orally for a like number of days and the fourth group received both promin and tubercle endotoxoid. The animals had been infected for twenty-four days before treatment was started.

<sup>4</sup> The index of infection is based on the arbitrary selection of the figure 100 as representing the maximal amount of tuberculous infection possible in any one animal.

The data obtained provide evidence in support of the following conclusions:

1. Tubercle endotoxoid failed to reveal any deterrent or therapeutic effects on tuberculosis previously established in guinea pigs.
2. Concurrent treatment with promin of another group of experimentally infected guinea pigs resulted in definite suppression of the disease.
3. Slightly more effective therapeutic results were observed in a group of experimentally infected tuberculous guinea pigs that received both promin and tubercle endotoxoid than were obtained in the group which received promin alone.

#### SUMARIO Y CONCLUSIONES

Empleando endotoxoides tuberculosos facilitados por Grasset, se realizaron experimentos para determinar el efecto de esta sustancia sobre la evolución de la tuberculosis experimental en el cobayo. Tomando cuatro grupos de 16 cobayos cada uno, todos fueron inoculados subcutáneamente con 0.001 mg. de una cepa humana del bacilo tuberculoso (H37Rv), y se dejó un grupo sin tratar, como testigo. Un grupo recibió endotoxoides tuberculosos solamente dos veces por semana durante 182 días; otro grupo recibió promina por vía oral durante un número semejante de días, y el cuarto grupo recibió promina y endotoxoides tuberculosos. Los animales habían sido infectados 24 días antes de comenzar el tratamiento.

De la información obtenida se derivan las siguientes conclusiones:

1. El endotoxoides tuberculoso no reveló ningún efecto contrario o terapéutico sobre la tuberculosis previamente establecida en los cobayos.
2. El tratamiento concurrente con promina, de otro grupo de cobayos infectados experimentalmente, resultó en la supresión definitiva de la enfermedad.
3. En un grupo de cobayos infectados experimentalmente, que recibió promina y endotoxoides tuberculosos, observáronse resultados terapéuticos ligeramente más eficaces que los obtenidos en el grupo que recibió promina solamente.

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## NOTICE

### United States Public Health Service

#### Tuberculosis Control Division

##### *Two New Films Available on Administration of Mass Radiography Programs*

Two motion pictures on tuberculosis case-finding with miniature film mass radiography of the chest have just been completed for the U. S. Public Health Service, under the supervision of the Tuberculosis Control Division. The films demonstrate the techniques, the staff, procedures and equipment required for: (1) routine admission miniature film chest X-ray examination of all patients and personnel entering general hospitals; (2) miniature film mass radiography in community tuberculosis case-finding programs.

These are teaching and orientation films for an audience of professional, technical, or administrative personnel, or trainees, in the fields of medicine, public health, and hospital care. The film prints are 16 mm. size, black and white, with sound.

##### ROUTINE ADMISSION CHEST X-RAY IN GENERAL HOSPITALS

This film was photographed at University Hospital, Ann Arbor, Michigan. After an introductory statement about mass radiography by Dr. Fred J. Hodges, Professor, Department of Roentgenology, the film shows the step-by-step sequence of routine miniature film chest X-ray service for all patients admitted to the hospital or clinic. Case histories are reenacted and the corresponding X-ray films shown, to demonstrate the efficiency and benefits of this service. Animated drawings are used to illustrate the operation of the phototimer, to present case-finding statistics, and to demonstrate the physical arrangement of the admission chest X-ray unit. Details of record keeping, of film processing, interpretation, reporting, and filing are presented. The film demonstrates the danger of undiagnosed tuberculosis in hospitals. It highlights the benefits of early diagnosis for treatment of nontuberculous as well as tuberculous pathology found in hospital patients as a group, when all receive routine chest X-ray examination. The compactness, simplicity, speed and efficiency of miniature film chest X-ray equipment are shown. Throughout the film are many scenes demonstrating the advantages, benefits, and practicability of miniature film X-ray equipment and routine admission chest X-ray service.

##### TECHNIQUES OF GROUP CHEST X-RAY SERVICES

This film provides community health leaders and public health personnel with an up-to-date and detailed procedure outline for administration and operation of miniature film mass radiography case-finding programs. It features the basic and the newest developments in equipment and techniques. The film reenacts a conference attended by representatives of official and voluntary health agencies, professional groups, labor and management, and then illustrates

the functions and responsibilities of each—before, during, and following a typical mass radiography project. The second half of the film depicts an actual mass radiography project in operation—from the time it is first planned and scheduled, until it is completed and all reports tabulated. The major theme is the importance of organization, planning, and teamwork. Photography and narration highlight all the details that must be carefully considered by the responsible administrative group and by the operating personnel.

*Loan and Purchase Data:* After July 1, 1946, a print of each film will be available for short-term loan from Tuberculosis Control Division Consultants in the District Offices of the U. S. Public Health Service. Prints may be purchased from Castle Films, Inc., 30 Rockefeller Plaza, New York 20, N. Y.

Routine admission chest X-ray in general hospitals.....	\$23.00 per print
Techniques of group chest X-ray services.....	\$21.00 per print

# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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**Pulmonary Calcification and Negative Tuberculin Reaction.**—The literature relating to the presence of calcified pulmonary lesions without tuberculin sensitivity is reviewed. This type of calcification is particularly prevalent in the eastern slope of the Mississippi river basin ranging from 27 to 83 per cent in different states of this region. Only 10 to 50 per cent of these calcified lesions are accompanied by tuberculin sensitivity. The absence of tuberculin allergy in these instances has been interpreted as evidence for the non-specificity of the tuberculin reaction. However, Gass observed the development of calcified lesions in children in Tennessee without concomitant tuberculin sensitivity. Since children in this section failed to react to coccidioidin, infection with *Coccidioides immitis* as the agent responsible for the calcification was excluded. Independently of Palmer's observation of the rôle of *Histoplasma capsulatum* in pulmonary calcification, it was found in a study of 181 Tennessee children that the incidence of positive reactions to histoplasmin is more frequently correlated with pulmonary calcification than with positive tuberculin reactions. Thus at the age of 5 to 9, 63 per cent had positive histoplasmin reactions, 38 per cent showed pulmonary calcifications and only 14 per cent had positive tuberculin reactions. In a known case of infection with *Histoplasma capsulatum* a positive reaction to histoplasmin developed. These observations do not exclude other agents as responsible either for the pulmonary calcifications or for the positive histoplasmin reactions because of the possibility of cross reactions between various fungi. They nevertheless

suggest a possible etiologic relationship between benign histoplasmoses and pulmonary calcification and point directly to the likelihood that much pulmonary calcification observed in this region is of nontuberculous origin.—*Pulmonary Calcification in Negative Reactors to Tuberculin*, A. Christie & J. C. Peterson, *Am. J. Pub. Health*, November, 1945, 35: 1151.—(M. B. Laurie)

**X-ray Findings in Negative Tuberculin Reactors.**—Photoroentgenograms of 2,000 individuals with negative Mantoux tests revealed presumably tuberculous lesions in 40 cases (2 per cent). On closer analysis certain findings, such as hilar adenopathies and widening of the mediastinum, had to be considered as nontuberculous. The remaining cases (0.25 per cent) were represented by tracheobronchial adenopathies, gangliopulmonary processes and infiltrations. Further studies in some of the latter cases showed, later on, a positive Mantoux test, thus proving the existence of a preallergic phase. The overall results of these investigations showed that the preallergic phase has to be taken into consideration in age groups below 20 years; after this age it can be disregarded. In 196 cases pleural and pulmonary changes were found, such as pleural thickening, indurations, calcifications, which could be considered as tuberculous sequelae. The negative tuberculin reaction in these cases can be interpreted as latent allergy (Sayce), an expression of biological healing. The negative tuberculin test acquired great diagnostic importance in one case of pulmonary mycosis, in one case of bronchiectasis and in one case of hydatid cyst.—

*Imagen radiografica pulmonar de torax de dos mil reactivos negativos a la tuberculina*, A. R. Gines & S. D. Martinez, *Hoja fisiol.*, September, 1944, 4: 241.—(L. Molnar)

**Negative Tuberculin Reactions.**—Negative tuberculin reactions are obtained under various conditions. First, in persons who have not had a tuberculous infection (normergy). The number of such persons in countries of massive tuberculinization is small; the incidence of negative tuberculin reactions diminishes with age. In persons who had been exposed to infection, or in presence of pulmonary findings resembling those usually observed in primary infection, a preallergic condition may be suspected. The incidence of this condition is certainly small: in 2000 cases of negative tuberculin reactions the author has definitely proved the existence of a preallergic status in only 0.45 per cent. Finally, it has been demonstrated that with the biological healing of the tuberculous process positive tuberculin reactions may turn negative. Out of 269 cases of negative tuberculin reactions there were 24 with the presence of calcifications. This condition is called "latent allergy" (Sayé) or "extinction of allergy." In these cases the tuberculin reactions are negative, but the individual has maintained a certain capacity to reaction, which is manifested by a shortening of the preallergic condition after a new exposure. Latent allergy is called by some authors "secondary positive anergy," in contrast to the secondary negative anergy which is said to be characteristic of the terminal stages of tuberculosis. The author's experience does not bear out the assumption that such a condition exists and he feels that the question should be reinvestigated.—*Interpretacion de las reacciones tuberculinicas negativas*, A. R. Gines, *Hoja fisiol.*, December, 1944, 4: 325.—(L. Molnar)

**Loss of Tuberculin Sensitivity.**—The case of a 13 year old boy is presented in whom a primary pulmonary tuberculosis had been diagnosed. The skin test was positive at that time, but repeated subsequent tests proved

that the skin sensitivity decreased progressively until five years later the skin test was and remained negative.—*Extinction des réactions tuberculiques après une primo-infection*, M. Chevalley, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1940, No. 38.—(G. Simmons)

**Histoplasmin Reactors.**—Histoplasmin is a sterile broth filtrate of a culture of *Histoplasma capsulatum*; blastomycin is prepared from broth cultures of *Blastomyces dermatitidis*, coccidioidin from cultures of *Coccidioides immitis*, and haplosporangin from cultures of *Haplosporangium parvum*, a fungus causing pulmonary disease in wild rodents. Histoplasmin injections had no toxic effect on guinea pigs and mice. Normal guinea pigs did not react to intracutaneous reactions of histoplasmin and blastomycin. Of 39 guinea pigs with experimental histoplasmosis, 32 reacted to histoplasmin in a dilution 1:100; of the remaining 7, 5 reacted to a 1:10 dilution. Nine rabbits with experimental histoplasmosis reacted to histoplasmin. Of 8 guinea pigs experimentally infected with *Blastomyces dermatitidis*, 8 reacted to histoplasmin, 7 to blastomycin and one to coccidioidin. Of 7 experimentally infected with *Coccidioides immitis*, 2 reacted to histoplasmin, and 6 to coccidioidin. Of 7 guinea pigs experimentally infected with *Haplosporangium parvum*, 6 reacted to histoplasmin, 6 to blastomycin, 4 to coccidioidin, and 5 to haplosporangin. Of 9 rabbits with experimental histoplasmosis, 9 reacted to histoplasmin and 8 to blastomycin. One hundred and thirty-six hospitalized persons, of whom 69 had atypical pulmonary lesions, were tested. Fifty-five (40.4 per cent) reacted to histoplasmin, 35 (25.7 per cent) reacted to blastomycin and 34 (25 per cent) reacted to both antigens. A positive histoplasmin reaction may be due to sensitization to either *Histoplasma capsulatum*, *Blastomyces dermatitidis* or some other unknown antigenic agent.—*Studies of the Role of Fungi in Pulmonary Disease. I. Cross Reactions of Histoplasmin*, C. W. Emmons & B. J. Olson, *Pub. Health Rep.*, November 23, 1945, 60: 1833.—(G. C. Leiner)

Albert Calmette.—A short biography and a moving tribute to Albert Calmette whose last injunction to the author was, "My son, I am dying. Take care of my wife. Do not leave for America. Fight for BCG."—*La inmunidad antituberculosa y la vacunación con el B.C.G.*, A. Sáenz, *Rev. tuberc. Habana*, January-March, 1945, 9: 5.—(R. Kegel)

**BCG Vaccination.**—During the last five years, increasing interest has been aroused in vaccination. Recent work has proved the harmlessness of BCG for man, but the ideal method of administration has been in doubt. Specific protection against virulent infection is produced only when BCG vaccine is used parenterally. There is no biological test available in man to disclose the degree of acquired protection. Earlier investigators have arrived at the conclusion that oral administration was of little value, there being only 7.6 per cent conversion of tuberculin reaction. Subcutaneous injection was then begun in 0.25 mg. doses with resultant extensive local necrosis; reduction of dosage to 0.01 mg. resulted in 90 per cent tuberculin conversion in a three months' period. This method was still accompanied by a 30 per cent incidence of suppurating abscesses of regional lymph nodes. Intracutaneous injection of 0.01 to 0.05 mg. resulted in 93 per cent positive reaction in six to seven weeks. It was necessary, however, to revaccinate 23 per cent of these subjects before conversion occurred; the incidence of suppurating abscesses between 1939 and 1942 was between 23.6 per cent and 10.4 per cent, respectively, by the use of this method. Birkhaug repeated the work of Rosenthal, using 5 mg. per cc. of BCG with a series of guinea pigs, and found that the regional lymph nodes became palpably enlarged for five to six months after vaccination; the tuberculin test became positive in all animals in four weeks and remained so for fourteen months. The degree of tuberculo-resistance was measured by infecting 12 animals with 0.001 mg. of a highly virulent human tubercle bacillus and 12 control animals. All animals were killed in eight weeks and their tuberculous lesions com-

pared quantitatively according to the weight and volume of various organs. Control animals presented advanced caseo-necrotic lesions at the inoculation site and adjacent lymph nodes, numerous tubercles in the spleen and scattered tubercles in the liver and lungs. The vaccinated animals presented a small infiltrated area at the inoculation site without abscess; there were slightly enlarged adjacent lymph nodes and no macroscopic lesions in the internal organs or lymph nodes. Birkhaug, in 1940, was next encouraged to transfer the multiple puncture BCG vaccination to man. A group of 246 adults and 38 children were vaccinated by the use of an 8-needled apparatus. The vaccine suspension contained 5 mg. BCG per cc. The initial traumatic swelling subsided in three to five days and red papules developed during the second week. In four to seven weeks, the papules began to desquamate and disappear without evidence of ulceration. Occasionally the axillary lymph nodes on the vaccinated side were tender and palpably enlarged. When individuals in an allergic state were vaccinated, the papules became intensely red and markedly elevated, later became confluent and pustulated and signs of intoxication became evident; 2 cases of erythema nodosum are thought to have been provoked by vaccination in allergic individuals. Of the vaccinated group, 93.7 per cent became tuberculin-positive in two weeks and 100 per cent became positive in four weeks and remained so for one year or more. In 1943, approximately 1,500 persons were vaccinated by the percutaneous method, using the automatic apparatus. Ninety-eight per cent positive tuberculin reactions with 1 mg. OT occurred two months after vaccination.—*Protective Value of the Intracutaneous and Percutaneous Methods of BCG Vaccination*, K. Birkhaug, *Acta med. Scandinav.*, 1944, 117: 274.—(E. R. Loftus)

**BCG Vaccination.**—The author, a former associate of Calmette, writes of the development of the bacillus Calmette-Guérin from a bovine tubercle bacillus cultivated upon a bile-enriched medium for 230 generations during three years. This bacillus had lost all power



to cause disease in animals and man but was antigenetically similar to virulent tubercle bacilli. After innumerable animal experiments Calmette in 1921 began to give BCG orally to vaccinate the infants of tuberculous parents. The Pasteur Institute undertook the wide-spread distribution of BCG in 1926. In the next decade over one million French children were vaccinated. The total number of persons vaccinated in Europe, Asia and America is now over ten million. While the oral route of vaccination is official in France, the subcutaneous, intracutaneous, multiple puncture and scarification methods are used in some countries. The efficacy of BCG is proved by numerous reports from all over the world which agree in showing a reduction of the mortality from tuberculosis among vaccinated infants to one-fourth or one-fifth that of nonvaccinated infants. The tuberculous mortality rates of vaccinated nurses, soldiers and medical students are most favorably influenced by BCG.—*La vacunación preventiva de la tuberculosis por el B.C.G., sus bases experimentales y su desarrollo actual*, A. Sáenz, *Rev. tuberc. Habana*, January–March, 1945, 9: 23. —(R. Kegel)

**BCG Vaccination.**—A review of the work of the past two decades on antituberculous vaccination with Calmette's BCG in infants, adolescents and adults confirms its innocuousness and efficacy. The immunity it confers to both animals and humans is not absolute. The more rigorously the possibility of virulent infection is excluded before and immediately after vaccination with BCG, the better are the results. It is the task of the future to examine with exactitude the conditions under which vaccinated persons develop tuberculosis and to determine the limits of BCG's effectiveness. In North America, England and New Zealand, tuberculosis mortality rates are very low as contrasted with rates of 200 to 250 per 100,000 in Central and South America. The adoption of North American control measures by Latin America is urged but these measures, because of their slow results, should be supplemented by vaccination with BCG. If recent

studies on the efficacy of revaccination every two to three years are confirmed we may expect a decisive reduction in the tuberculosis mortality rates in the next twenty to thirty years.—*La vacunación antituberculosa de Calmette-Guérin B.C.G. 1924–1944*, L. Sáys, *Rev. tuberc. Habana*, January–March, 1945, 9: 52. —(R. Kegel)

**BCG Vaccination.**—The possibility of antituberculous vaccination through the respiratory route was studied. Twelve guinea pigs were held in small glass cages and exposed to a BCG aerosol (containing 0.06 to 0.07 g. bacilli) for thirty to sixty minutes on one to three occasions. Fifty per cent of the animals showed a positive tuberculin test after forty-three days, 75 per cent after fifty days, and 100 per cent after eighty days. The tuberculin allergy, however, proved to be of less than one year's duration. In a simultaneous study vaccination with BCG aerosol was attempted on 12 children under two years of age. The time of exposure was one hour in fractionated nebulizations of ten minutes. Each child received three sessions with one day's interval. The dose amounted to 0.09 g. or 0.18 g. at each session. No subsequent complications were noted. All children had been kept under strict isolation at least five weeks before vaccination and were not released before the appearance of a positive tuberculin reaction. In 4 cases the period of observation was insufficient. One case showed persistently negative tuberculin reactions, even after three subsequent intracutaneous administrations of 0.1 mg. of BCG. One case was discovered to have received a previous dose of BCG and became tuberculin-positive two weeks after vaporization, a result which permitted no conclusions. The 6 remaining cases showed appearance of a positive tuberculin reaction forty to sixty days after inhalation of the stronger suspension, and approximately five months after inhalation of the weaker suspension. In all cases the chest X-ray remained negative following vaccination.—*La vaccination antituberculeuse par les voies respiratoires. Aérosols et brouillards de BCG*, J. Troisier, J. Le Melletier & J. Sifferlen,

*Ann. Inst. Pasteur, January-February, 1944, 70: 53.*—(V. Leites)

**Bucconasal Administration of BCG.**—The authors have modified the technique of Etchemendigaray for bucconasal administration of BCG vaccine. They use 0.03 g. of BCG suspended in 3 cc. of liquid. This dose is divided in three portions and given by spray within a week. Fifty-six children of more than 6 years of age were tested. Forty-three children could be followed up. Of those, 37, or 86 per cent, developed positive tuberculin tests in some cases after nineteen days, but generally around the thirtieth day. This method compares favorably with the administration of BCG by mouth or subcutaneously and is hardly inferior to the intracutaneous or multiple puncture method. It has a high power of allergization and it is not harmful. But it is still not a practical method as it takes too long a time to apply the vaccine by spray and requires the help of at least one assistant. It is impractical for children under 6 years. The danger of inhalation of BCG vaccine by the administering physician is pointed out. Experiments with this new method in 10 animals did not result in any allergy within three months.—*El metodo bucco-nasal de administracion de la vacuna B.C.G., R. F. Vaccarezza, A. R. Aréna & A. Brisco C., An. Cáted. de pat. y clin. tuberc., June 1, 1944, 5: 194.*—(W. Swienty)

#### Pathological Changes Produced by BCG.—

BCG was applied by the scarification method and the cellular processes at the site of application were studied. Slides made a few minutes after scarification showed the wound covered with numerous bacilli and invaded by a lymphatic fibrinous exudate. There was no cellular reaction as yet. Five hours after scarification the appearance of polynuclear leucocytes was noted. The wound was filled with a fibrinous coagulum containing part of the bacilli, the other part of which had been carried by the leucocytes towards areas of healthy tissue. From the third day on there was disappearance of leucocytes, which were replaced

by numerous monocytes containing bacillary bodies in a stage of multiplication. In the course of the second week the lesion showed enlargement through increase in monocytes and the appearance of numerous epithelioid cells. Giant cells and lymphocytes were noted at this stage. The bacillary bodies were intracellular and showed marked multiplication. From the third week on the number of bacilli decreased through some unknown mechanism, although the lesion kept on enlarging up to the sixth week, consisting mainly of epithelioid and some giant cells. From that time there was retrogression. Eventually at the site of the scarification there was an absolutely intact epidermis with a few underlying fibroblasts.—*Les modifications anatomo-pathologiques provoquées par le BCG au niveau des scarifications cutanées, J. Bretey, Ann. Inst. Pasteur, September-October, 1942, 68: 452.*—(V. Leites)

**Treatment of Tuberculosis with BCG.**—In order to study the effect of BCG administered by cutaneous scarification on guinea pig tuberculosis, the following experiments were done: (1) Twelve guinea pigs were infected with virulent tubercle bacilli. Eight of these were vaccinated with BCG twice weekly. All animals were sacrificed after eight weeks. In the treated animals there was a slight retardation of the generalization of the lesions. (2) Twenty-nine guinea pigs were infected with virulent tubercle bacilli. Twelve of these were vaccinated with BCG on the first, fifteenth and thirtieth day. All animals were sacrificed after six weeks. There was no difference in the extent of the disease between the treated animals and the control group. (3) Twelve guinea pigs were infected with virulent tubercle bacilli. Seven of these were vaccinated by BCG two days later. The animals were sacrificed after eight weeks. There was no difference between the treated animals and the controls. (4) Twelve guinea pigs were vaccinated with BCG and five weeks later infected with virulent tubercle bacilli. Seven of these were vaccinated with BCG after two days, six weeks, eight weeks and twelve weeks. The animals were sacrificed four months after they

had been infected. The treated animals had slightly fewer lesions in the liver and in the lungs than the controls. (5) Twenty guinea pigs were vaccinated with BCG and ten weeks later infected with virulent tubercle bacilli. Five of these received 6 vaccinations with BCG in the following six months. Five animals were vaccinated with heat-killed human tubercle bacilli. Five animals were treated with subcutaneous injections of BCG. Five animals remained as controls. All guinea pigs were sacrificed five months after they had been infected. No difference in the extent of the disease was seen between the four groups. (6) The same experiment was done on 20 guinea pigs with the only difference that they received subcutaneous injections of BCG. One group remained as control and three groups were treated exactly as those in the preceding experiment. No difference was seen between the different groups.—*Influence exercée sur la tuberculose du cobaye par le BCG administré par sacrifices cutanées*, L. Nègre & J. Bretey, *Ann. Inst. Pasteur*, May-June, 1945, 71: 161.—(G. C. Leiner)

**Sterilization of Tuberculous Lesions.**—Sterilization of tuberculous lesions and extinction of tuberculin sensitivity are never observed in the usual guinea pig experiments, even with minimal doses of virulent bacilli. Since tuberculosis of the guinea pig is invariably fatal, no conclusions should be drawn concerning any form of human tuberculosis and especially not the latent form of bacillary infection in man. It is only in this latter form that Saenz, Ameuille and Canetti have described a frequent sterilization of lesions. However, experimental tuberculosis of the guinea pig can be made comparable to latent tuberculosis in man by inoculating guinea pigs with extremely attenuated bacillary strains. Administration of BCG to guinea pigs was found to reproduce anatomically and clinically latent tuberculosis (by latent pulmonary tuberculosis is understood the presence of a primary complex in otherwise healthy individuals). In the guinea pig experiments carried out in collaboration with Canetti com-

plete sterilization of lesions was found after a maximum of three months with a dose of 1 mg. of BCG, and after five months with a dose of 10 mg. After a dose of 1 mg. of BCG it is rare that tuberculin sensitivity persists after a period of ten months. After 10 mg. the extinction takes place between the fifteenth and twenty-fifth month. There appear to be great individual variations in the time of disappearance of tuberculin sensitivity in animal experiments, suggesting similar conditions in human tuberculosis. A rather long interval was found between the moment of sterilization of lesions and disappearance of tuberculin sensitivity. The lesions are found sterile from the third to fourth month on, whereas tuberculin reactivity hardly disappears before the tenth or twelfth month, often even much later. This fact leads to the conclusion that during a long period of its existence the tuberculin reaction has another substratum than the presence of living tubercle bacilli in the organism. This substratum might be some colloidal modification of the cellular protoplasm produced by the sensitizing antigens, persisting long after the source of these antigens is exhausted. It is probable that similar conditions exist in man. Latent tuberculous foci are usually sterile when the stage of calcification is reached, whereas the tuberculin reaction persists much longer. In view of this fact it becomes impossible to affirm that every tuberculin reactor may develop active pulmonary tuberculosis without new infection. In another series of experiments guinea pigs were treated as above and reinfected with a virulent strain after their tuberculin sensitivity had subsided. The reappearance of tuberculin sensitivity was now markedly accelerated as compared to controls, and it was highly positive. These findings demonstrate that, after complete extinction of tuberculin sensitivity of the skin, there still persists a state of allergy in the organism in the sense of a modified reactivity. Thus, skin sensitivity to tuberculin is not the only expression of tuberculous allergy. The phenomenon of acceleration of re-sensitization seems also to exist in man as some observations indicate.

It is finally emphasized that the above findings do not speak against the protective value of BCG, the protection created by the allergic state and the allergic state itself not being identical.—*Quelques considérations expérimentales sur les notions de stérilisation des lésions tuberculeuses*, A. Saenz, *Rev. de la tuberc.*, 1939-40, 5: 1888.—(V. Leites)

**Intracerebral Inoculation of Tubercle Bacilli.**—Ten young monkeys from Guinea were inoculated intracerebrally with 0.05 mg. of tubercle bacilli of various strains. No difference was found in the pathogenic effect of human and bovine type bacilli. Death occurred with both strains three to four weeks after inoculation following a short period of prostration and somnolence. The local reaction appeared early and was of marked severity. There was involvement of the major part of the meninges and the parenchyma of the inoculated hemisphere. The cerebral parenchyma was the site of extensive cellular infiltrates consisting mainly of polynuclear leucocytes, forming real nodular abscesses which showed varying degrees of confluence. No typical tubercles were found in the parenchyma. Giant cells were rare or absent. There was no evidence of caseous necrosis. The vascular reaction was very marked consisting in new-formation of numerous capillaries and medium sized vessels in a state of dilatation and endothelial proliferation. There was marked proliferation of the glia elements. The accompanying meningitis, which was always present, showed histologically a more typical picture of tuberculosis. There was histiocytic and lymphocytic infiltration with tubercle formation. Acid-fast bacilli were scant in the infiltrates consisting of leucocytes and more numerous in the histiocytic and epithelioid areas. Avian type bacilli produced a different reaction, the encephalitic infiltrates consisting of histiocytes, lymphocytes and epithelioid cells. This strain did not produce any dissemination of tuberculosis to other organs. Animals inoculated with human and bovine type bacilli showed tubercle formation in the tracheobronchial lymph nodes, lungs,

liver and spleen. Particular emphasis is laid on one case inoculated with a human type of very low virulence, isolated from a case of lupus. A large multilocular abscess was found, consisting of leucocytes in the state of fatty degeneration, surrounded by a zone of sclerosis and a zone of cleavage. There was no histological evidence of tuberculosis and no acid-fast bacilli were found. The animal showed clinically no downhill course and was killed after six months for autopsy. An analogy is seen in this case to a certain number of cerebral abscesses in man which come to operation and in which histological and bacteriological examination fails to demonstrate tuberculosis. The hypothesis is ventured that these abscesses may be due to tubercle bacilli of very low virulence, which have been gradually destroyed by local tissue reactions.—*Sur l'inoculation intracrêbrale de bacilles tuberculeux et paratuberculeux chez les singes inférieurs*, I. Bertrand & J. Bablet, *Ann. Inst. Pasteur*, March, 1942, 68: 175.—(V. Leites)

**Tuberculous Infection with One Bacillus.**—The problem was studied whether one single bacillus is capable of producing tuberculosis in guinea pigs. The experiments were carried out with the micromanipulator of Peterfi. The site of inoculation was an incision in the lumbar region. The bacilli which had been isolated under the micromanipulator were suspended in saline and injected with the micropipette. All animals had a negative tuberculin reaction at the onset of the experiment. Nine guinea pigs were inoculated with one bacillus and one animal received three bacilli. Tuberculin reactions were performed repeatedly at regular intervals during the following three months. Five out of the 9 animals having received one bacillus developed tuberculosis, the starting point of which was the site of inoculation as confirmed by autopsy. The tuberculin reaction became positive during the second month after infection. The 5 other guinea pigs did not develop manifest tuberculosis but showed atypical allergic reactions as evidenced by a transitory and

attenuated tuberculin reaction. In one guinea pig the tuberculin reaction was doubtful. These animals were later utilized for other experiments with virulent infection and reacted in the same way as vaccinated animals.—*Expériences d'infection par un seul bacille tuberculeux isolé au micromanipulateur, J. Bretey, Ann. Inst. Pasteur, November-December, 1944, 70: 557.*—(V. Leites)

**Variations of the Koch Phenomenon.**—Tuberculosis was induced in guinea pigs with 0.01 mg. of human type bacilli. After establishment of tuberculin allergy the response to regularly repeated reinfections was studied. The interval between the reinoculations varied between one and eight weeks. The dose was 0.1 to 1.0 mg. The following reactions were found: (1) In a small number of cases each reinoculation was followed by a typical Koch phenomenon. (2) More frequently an attenuation of the Koch phenomenon was observed, which was in some cases followed by its complete disappearance. (3) In a third group of cases irregularity of the reactions was noted, the animals reacting to the reinoculations alternately with a typical Koch phenomenon and with a simple infiltration. The reason for these fluctuations could not be found. (4) Another group of animals reacted on some occasions with a Koch phenomenon, on others with the formation of an abscess containing tubercle bacilli. The conclusion is drawn that the response to repeated reinoculations is variable and that the Koch phenomenon represents by no means a constant mode of reaction.—*Les modalités du phénomène de Koch au cours de la période allergique de la tuberculose du cobaye, P. Gastinel & H. Brocard, Ann. Inst. Pasteur, July-August, 1945, 71: 240.*—(V. Leites)

**Lesions Due to Dead Tubercle Bacilli.**—Intratesticular inoculation of guinea pigs with dead tubercle bacilli incorporated in vaseline oil produced pulmonary lesions of greater extent than subcutaneous inoculation. The lesions produced by human and bovine strains were identical. After intratesticular inocula-

tion of rabbits with dead bovine bacilli death occurred within thirty to sixty days with massive pulmonary lesions consisting of large areas of caseation and hemorrhagic infiltration. The lungs were markedly hypertrophic. Inoculation of dead bacilli of the human type did not produce death and the pulmonary lesions were insignificant. With dead avian bacilli the pulmonary lesions were of moderate intensity, miliary and hemorrhagic in character. Death occurred frequently. The pulmonary lesions produced by all these strains resembled closely the lesions produced by the corresponding bacilli in the living state. Separate injection of dead bacilli intravenously and of vaseline oil intratracheally, intraperitoneally, or into the testicle, often produced lesions which were in all respects comparable to the ones above described. These lesions developed even if the bacillary injection was performed from five to thirty days after the instillation of oil. Intratesticular injection of dead BCG in vaseline oil produced pulmonary lesions which were only slightly less extensive than those produced by dead bovine bacilli of virulent strains. Intratesticular inoculation of living BCG in oil had the same effect as dead BCG. Living human bacilli administered in the same way did not give stronger reactions than dead human bacilli. It is concluded that the physico-chemical constitution is of the greatest importance in determining the pathogenic power of tubercle bacilli.—*Les propriétés pathogènes des bacilles tuberculeux morts, enrobés dans l'huile de vaseline et injectés par voie testiculaire. Leur apport aux notions de spécificité et du virulence du bacille tuberculeux, A. Saenz & G. Canetti, Ann. Inst. Pasteur, July, 1940, 65: 18.*—(V. Leites)

**Artificial Pleural Adhesions.**—Many surgical interventions require the presence of adhesions between the parietal and the visceral layers of the pleura. Thoracotomy for pulmonary abscess, hydatid cyst, the Monaldi operation, sometimes lobectomy and pneumonectomy, cannot be performed without there being previous adhesions established. Chronic or recurrent spontaneous pneumo-

thorax, nonexpandable artificial pneumothorax as well as pleural exudates also make it necessary to obliterate the pleura cavity. Extrapleural methods to establish adhesions are based on the principles to irritate the serosa with certain substances or foreign bodies and cause a local inflammatory reaction. The adhesions so obtained are generally partial. The intrapleural method may establish a complete symphysis between the two layers of the pleura. This method is based on the principle of causing an aseptic pleurisy. This may be obtained by insufflation or injection of powders, of biological products or irritating chemical substances. There is general consent that the more intense the reaction as shown by pain and temperature, the greater the danger of sudden exudates and pulmonary complications. If the reaction is slight, the adhesions are either too few or even completely absent. It is necessary to withdraw the air by continuous suction immediately after installation of the irritating substance so that both layers of the pleura stay in intimate contact. This is easy if the lung can readily be expanded, but is difficult to obtain in the presence of fluid or if there is a thick fibrotic pleura. The authors have used iodized oil in a case of spontaneous pneumothorax and bronchopleural fistula with complete cure. In another case of spontaneous pneumothorax in an old syphilitic, quinine chlorhydrate and urea were successful after injections of blood, talcum and gomenol had been tried unsuccessfully. In a third case, a therapeutic pneumothorax was discontinued but the lung did not reexpand. Six injections of sodium morrhuate established enough adhesions for obliteration of the pleural space. These observations show that the same substance may be successfully employed in one case and may be unsuccessful in another. In all 3 cases, a more or less abundant exudate, which was well tolerated, preceded the pleural fusion. A reactivation of the tuberculous lesion by the irritating substance was not observed in the third case. The authors believe that persisting fluid in the pleural cavity makes an artificial pleural fusion impossible. A

pleurisy with effusion of long standing changes the structure of the pleura. A marked tolerance is established against any substance introduced for irritating purposes. To obtain adhesions the concentration of these substances would have to be so strong that serious damage would be done to the tissue. In these cases a thorocoplasty is inevitable.—*Consideraciones sobre sinfisis pleural artificial, A. C. Artagaveytia & L. E. Matos, Rev. de tuberc. d. Uruguay, November 4, 1944, 12: 237.*—(W. Swienty)

**Paratubercle Bacilli.**—A comprehensive review of the literature on paratubercle bacilli is given. The original contribution consists in studies on the modifying effect of fatty substances on lesions produced by paratubercle bacilli in laboratory animals (guinea pigs, rabbits, white rats, chickens). Seven strains of paratubercle bacilli of different virulence were used. The first series of experiments were performed on guinea pigs with the bacillus P, isolated from the pus of a cold abscess. Subcutaneous inoculation of a culture of P bacilli in a dose exceeding 1 mg. produced the formation of a small abscess which regressed spontaneously without involvement of the regional lymph nodes. With doses over 20 mg. cultural studies sometimes revealed the presence of bacilli in the parenchymatous organs, but no definite lesions were found. Inoculation of the same bacilli emulsified in paraffin oil produced different lesions. The local abscess appeared earlier and was more marked. An ulceration developed ten to fifteen days later with formation of an enormous chancre, persisting for two months. The regional lymph nodes showed hypertrophy and caseation. The spleen was slightly hypertrophic. The lungs showed granulations without caseation. The pus of the local abscess revealed numerous acid-fast bacilli. With intraperitoneal inoculation aqueous solution of P bacilli produced very slight lesions without tendency to dissemination. Inoculation of 1 to 5 mg. of bacterial culture in oily emulsion produced constantly very extensive lesions with subsequent death of the guinea

pigs within thirty days. The majority of the animals died between the eighth and fifteenth day. In all cases the blood culture was positive for paratubercle bacilli five to six days after inoculation. Autopsy revealed consolidations in the lungs, caseous-pneumonia in nature. The tracheobronchial lymph nodes were hypertrophic and partly caseous. An abundant pleural effusion was always present. There was a marked peritonitis with formation of thick false membranes. There was hypertrophy and caseation of the mesenteric lymph nodes. All lesions showed the presence of acid-fast bacilli, often grouped around a drop of oil. Mixtures of paraffin oil and bacterial culture were also injected into the lymph nodes. Death occurred within eight to thirty days. The lungs showed similar lesions as with intraperitoneal injection. The lymph nodes showed massive caseous lesions. Instead of injecting mixtures of bacteria and oil another series of experiments utilized the method of separate administration of these two substances. The result was the development of extremely extensive lesions at those points in the organism where bacilli and oil came in contact. Thus, subcutaneous injection of oil and simultaneous intravenous injection of bacilli produced a large caseous abscess at the site of the oil injection with involvement of the lymph nodes. Necrotic granulation tissue was present in the lungs. Similar experiments were conducted with separate injection of oil and bacilli by various routes (intraperitoneal injection of oil with simultaneous intravenous injection of bacilli, intraperitoneal injection of oil and intravenous injection of bacilli two weeks later, intravenous injection of bacilli and subsequent intratracheal injection of oil). In all cases the activating influence of paraffin oil was evident: the paratubercle bacilli were found to establish themselves and to multiply considerably at the site of the oil deposits, producing extensive caseous lesions. No similar lesions were found in controls in which oil alone or bacilli alone had been injected. Similar results as in guinea pigs were observed in the rabbit and the white rat. The chicken showed reac-

tions of much lesser degree. Other fatty substances than paraffin oil were also found to have a stimulating effect on the pathogenicity of paratubercle bacilli. Lesions produced by paratubercle bacilli in the presence of fatty substances were found to have a rich bacillary content in contradistinction to lesions produced by bacilli in aqueous solution. The stimulating effect on bacterial multiplication was further confirmed by the following experiments: very small doses of P bacilli emulsified in paraffin oil were inoculated. Aqueous solutions of 0.2 mg. and below did not produce any pathological effect; 0.02 mg. in oily suspension produced death between the tenth and twentieth day with caseous lesions containing numerous bacilli. Doses of 0.01 and 0.0001 mg. rarely produced death of the animals, but they all showed pulmonary lesions rich in bacilli. The following assumptions are made to explain the mechanism of the stimulating effect of fatty substances on pathogenicity: (1) the oil extracts from the bacterial cell contain toxic substances of unknown chemical composition, (2) the incorporation of bacilli in fatty substances produces a slowing of bacillary disintegration and a more prolonged absorption into the organism, (3) increased toxicity of the bacterial effect due to additional irritation by the fatty substances themselves.—*Contribution à l'étude des bacilles paratuberculeux. I. Propriétés pathogènes, R. Laporte, Ann. Inst. Pasteur, November, 1940, 65: 282.*—(V. Leites)

**Lesions Due to Paratubercle Bacilli.**—Histological studies of lesions produced by paratubercle bacilli revealed a marked resemblance with true tuberculous lesions. This analogy was still more outspoken if sufficiently virulent paratubercle bacilli were inoculated in oily suspension, or if the bacilli, administered in saline, encountered in the lungs drops of oil, which had been introduced by another route. After parenteral inoculation the most important lesions were found in the lungs. Liver and spleen were relatively little involved. (Guinea pigs, rabbits and rats had been used for these investigations.)



The elementary pulmonary lesion was found to be of an exudative character with formation of pneumonic areas of various extent. The alveolar exudate consisted in the first stage of polynuclear cells, monocytes and large histiocytic elements, the latter becoming more and more prevalent. These histiocytes assumed in the course of the pathological process often an epithelioid aspect. They also were found to contribute to giant cell formation. Foci of epithelioid and giant cells showed often the typical structure of a tubercle with a surrounding area of lymphocytes and plasma cells. These lesions were found to be very poorly vascularized and showed areas of caseous necrosis. At all stages numerous acid-fast bacilli were present in the lesions. There was a marked tendency towards healing by fibrosis. Another comparison was made between paratubercle bacilli and true tubercle bacilli: the cytological reaction of the peritoneum was studied in the guinea pig after intraperitoneal inoculation of (1) virulent bovine bacilli, (2) BCG, (3) different strains of paratubercle bacilli. Comparison of diagrams indicating the time since inoculation and the cellular response showed that the general tendency of the reaction was the same in all investigated strains: (1) A first stage with predominance of polynuclear neutrophil cells. Intensity and duration of this phase were found identical, regardless whether virulent or paratubercle bacilli were used. (2) In the second stage the polynuclear cells were succeeded by monocytes with marked macrophagic properties. (3) A period of lymphocytosis followed, the duration of which depended on the virulence of the strain. Inoculation with a virulent strain produced very marked lymphocytosis which persisted until the death of the animal. With nonvirulent strains the lymphocytosis was of moderate degree and returned gradually to normal.—*Contribution à l'étude des bacilles paratuberculeux. 2. Histo-cytologie des lésions paratuberculeuses, R. Laporte, Ann. Inst. Pasteur, Décembre, 1940. 65: 415.—(V. Leites)*

**Virulence of Bovine Bacilli.**—Experiments were made with 5 strains of bovine tubercle bacilli derived from cases of human and animal tuberculosis. In analogy to the Calmette-Guérin procedure regular transplantations were made every fifteen days on bile-potato medium and the modifications of virulence were studied. Besides the known fact of progressively diminishing virulence in the course of these transplantations, a special phenomenon was noted consisting in a dissociation of pathogenicity for the guinea pig and the rabbit. Thus, after 30 to 50 transplantations these bovine strains became totally or partially nonpathogenic for the guinea pig, whereas they remained considerably virulent for the rabbit for a certain period of time. A second phenomenon was observed consisting in what the author calls the "toxic" quality of the pathogenic effect on rabbits. Intravenous injection of bovine strains before transplantation on bile-potato medium produces in the rabbit milary tuberculosis, especially of the lungs and kidneys. Inoculation with strains growing for more than one year on bile-potato medium produced death by tuberculosis of the "Yersin" type within twelve to twenty-eight days. On autopsy the lungs showed infiltrations in the interstitial tissue, consisting of polynuclear cells and histiocytes associated with intraalveolar edema. The kidneys showed simple "toxic" nephritis. There was no evidence of milary lesions anywhere, which are so characteristic of bovine infections in the rabbit. On the other hand, a resemblance is seen to the infection of the rabbit with the avian type bacillus, which also produces fatal tuberculosis of a more toxic character without any formation of typical tuberculous lesions in the organs.—*Modifications de la virulence du bacille tuberculeux bovin au cours des réensemencements successifs sur pomme de terre billée, F. van Deinse, Ann. Inst. Pasteur, March, 1941, 66: 191.—(V. Leites)*

**Tuberculosis in Cats.**—Ten strains of tubercle bacilli were isolated from cats which had died of tuberculosis. All colonies appeared to



be of the smooth type. After the first few transplantations on potato glycerine medium the colonies developed badly or not at all. Only the three oldest cultures (ten and eleven months) gave rise to colonies of the rough type. The interval between inoculation and appearance of the first colonies averaged four weeks. All these features were taken as evidence that the isolated bacilli belonged to the bovine strain. However, the proof of intravenous injection in the rabbit could not be carried out because of external circumstances. It is believed that tuberculous infection in cats is almost exclusively of the bovine type and originates from ingestion of products containing virulent bovine bacilli. The primary complex was mostly found in the gastro-intestinal tract. A review of the literature is given corroborating this view.—*Recherches sur la fréquence des différents types de bacilles tuberculeux dans l'infection spontanée du chat*, J. Verge & F. Senthille, *Ann. Inst. Pasteur*, February, 1942, 68: 114.—(V. Leites)

**Attenuation of Tubercle Bacilli.**—Experiments were performed with two strains of bovine and four strains of human type bacilli regarding the attenuating effect of bile-potato medium. Transplantations were made every fifteen days, according to the usual methods. The pathogenicity of bovine strains was evaluated by subcutaneous inoculation in the guinea pig and intravenous injection in the rabbit. In all cases a progressive and considerable lowering of the pathogenicity was found after prolonged growth on bile medium. The decrease of virulence developed gradually. At first there was progressive increase of the minimal lethal dose. Later, an identical massive dose produced less and less severe infection, the parenchymatous lesions becoming more circumscribed and showing increasing tendency towards healing. Finally there was a more and more strict blocking of the inoculated bacilli in the connective tissue and in the regional lymph nodes. However, the bacilli conserved a pronounced capacity of producing local lesions. It is believed that the attenuation by bile developed the more rapidly, the

weaker the pathogenicity of the strain at the onset of the experiment. Transplantations were carried out between the years 1927 and 1940. A detailed protocol is given of the periodically repeated animal inoculations throughout the years, demonstrating the progressive loss of virulence. Thus, in 1927, 0.01 mg. of the bovine strain "Vallée" inoculated intravenously into the rabbit and subcutaneously into the guinea pig produced death in the animals after two and a half months. In 1940, after 192 transplantations on bile-potato medium, 1 mg. of the same strain was injected in the guinea pigs. The animals remained well and were killed for autopsy after seven to eight months. No visceral lesions were found. There was a small abscess at the site of inoculation and a slight hypertrophy of the regional lymph nodes. Analogous results were found in all other experiments with growth on bile media. The bovine strain Vallée was furthermore cultured on potato medium in a 1 per cent solution of bile salts. The results regarding attenuation were comparable to those obtained on bile-potato medium. Attempts at anti-tuberculous vaccination were carried out with the attenuated strains. Four investigated strains (two bovine and two human types) all produced a definite resistance against a virulent reinfection, the results were however variable as to the degree of protection. The number of transplantations on bile media did not seem to be relevant for the vaccinating power of the attenuated cultures.—*Essais d'atténuation de bacilles tuberculeux par culture sur pomme de terre billée*, A. Boquet & Mme. A. de Grolier, *Ann. Inst. Pasteur*, January, 1942, 68: 5.—(V. Leites)

**S-forms of Acid-fast Bacilli.**—Blood cultures performed in 2 cases of active pulmonary tuberculosis in children yielded acid-fast bacilli resembling in form, size and cultural properties the S-form of tubercle bacilli. The culture was grown on egg medium according to the method of Löwenstein. These bacilli had numerous properties in common with tubercle bacilli: their inoculation produced tuberculous allergy in laboratory animals, as evidenced by

the development of a positive tuberculin reaction. Furthermore, these bacilli produced tuberculin. Skin tests performed with concentrated broth filtrates and with tuberculin gave identical reactions. These bacilli were not of the avian type, being nonpathogenic for the hen and the rabbit. Their main characteristic was their generally low virulence. In the guinea pig subcutaneous injection of 0.1 mg. produced no general nor local reactions. Subcutaneous injection of 1 mg. produced after two weeks a circumscribed nodule of pea-size, which showed no ulceration and went on to absorption. Inoculation of 10 mg. gave a more pronounced local reaction with formation of a caseous abscess the pus of which contained numerous acid-fast bacilli. Similar reactions were found in monkeys. The morphological resemblance of these S-forms with the true tubercle bacilli combined with their low virulence led the authors to investigations regarding their possible immunizing properties. Guinea pigs were inoculated subcutaneously and intraperitoneally with 1 and 10 mg. of S-type bacilli. Three months later they were given 0.01 mg. of a virulent human strain, which killed control animals after sixty to eighty days. It was found that the immunized animals survived much longer. If they were killed four to six months after the administration of the virulent strain, some of them appeared completely free of tuberculous lesions, others were hardly affected. If animals which have been immunized as above receive an intrapulmonary injection of virulent bacilli, one observes several months later only localized caseous lesions in the corresponding lung with a tendency to fibrosis, but no dissemination is noted. Liver and spleen remain free. In conclusion the nature of the S-form bacilli is discussed. The question is left open; the authors are, however, inclined to feel that they do not represent a separate species but are rather closely related to true tubercle bacilli.—*Étude des propriétés pathogènes et vaccinales de bacilles acido-résistants de type S (lisse) isolés du sang au cours de l'infection tuberculeuse évolutive chez de jeunes sujets, P. F.*

*Armand-Delille & O. Gysin, Ann. Inst. Pasteur, January, 1941, 66: 5.—(V. Leites)*

**Congenital Lung Malformations.**—A classification of congenital pulmonary malformations based on embryological criteria is presented. The bronchio-alveolar tree is of endodermic origin. In the first phase of its development, approximately by the sixth intra-uterine month, the bronchial tree is canalized. In the second phase the terminal bronchi lose their epithelium and become the alveolar sacs. Thus the alveoli represent the terminal part of the bronchial tree, adapted for gaseous exchange. Pulmonary malformations may be diffuse or local and are often associated with malformations in other organs. The X-ray diagnosis of pulmonary malformations is often uncertain because lesions of congenital or acquired nature may have a similar X-ray appearance. The authors differentiate between malformations that are always congenital and those lesions that may be of congenital or acquired origin. Among the former we have the agenesis of lung caused by the absence of a main bronchus. In these cases there is generally the absence of the pulmonary vessels on the affected side and they are often accompanied by cardiac malformations. An incomplete development of the bronchial tree is called hypoplasia of the bronchus. The arrest may occur at any stage of the bronchial development and correspondingly there are numerous and complex forms of malformations. Hypoplasia of a bronchus is usually associated with areas of broncho-alveolar agenesis and of bronchiectasis. The absence of one of the layers in the bronchial wall is called dysplasia. It is assumed that most of the cases of congenital bronchiectasis are due to some kind of dysplasia of the bronchial wall. The polycystic lung is a typical example of a process of congenital hyperplasia. The epithelial lining of the cysts is stratified, cylindrical, ciliated or nonciliated. Most cysts have no bronchial outlet. The clinical differentiation between polycystic lung and cystic or saccular bronchiectasis is difficult. Morelli has described a syndrome characterized by association of mal-

formations of various organs and systems. Among the processes that may be congenital or acquired, there is the group of subpleural blebs; they may be caused by scars or they may occur as congenital anomalies. The X-ray appearance of these varieties of blebs is similar regardless of the underlying pathological changes. Only histological examination may decide the etiology in such cases. Another group of processes that may give rise to diagnostic difficulties is that of bullous emphysema. The pathogenetic mechanism of this process may be inflammatory changes and scarring acting as a valve; in other cases dystrophía of the elastic tissue in some area of the lung is the cause of rupture of interalveolar septa; finally, vascular changes with consecutive tissue damage may also cause a breaking down of elastic tissue and the formation of bullous emphysema. The lung cysts of bronchogenic origin are frequently diagnosed as bullous emphysema because of similar radiological findings. The two processes show, however, sharply differentiated histological pictures: the lung cyst has an epithelial lining with the presence in its wall of cartilage and muscle, while the wall of the bullous emphysema is formed by connective tissue containing anthracotic pigment.—*Classification de las alteracions congenitas del pulmon*, P. Parriol & C. Epifanio, *Hoja tisol.*, December, 1944, 4: 307.—(L. Molnar)

**Lobar Pneumonia.**—Untreated lobar pneumonia in Holland is a milder disease than in the United States. Review of case histories of 356 cases treated between 1930 and 1938 shows that the mean fatality rate was 14.3 per cent. In those under 50 years of age the disease is usually mild, and no cases of death were recorded when the patient was under 50 and only one lobe was involved. The fatality rate rises sharply with age so that the mortality in patients over 50 is 43.5, whereas under 50 it is 8.2 per cent. Even though no treatment other than symptomatic was given, complications were few. Empyema was seen in 4.8 per cent of the cases, and pericarditis in 1.4 per cent. Sixty per cent of the patients had temperature

drop by crisis before the eighth day.—*The Course of Untreated Lobar Pneumonia in Holland*, N. Lubsen, *Acta med. Scandinav.*, June 23, 1942, 110: 465.—(H. Marcus)

**Obstructive Pulmonary Emphysema Associated with Pneumonia.**—Regional obstructive pulmonary emphysema in children following acute infections of the upper respiratory tract has only recently been recognized as a clinical entity. Two illustrative case histories are presented. The diagnosis depends upon the roentgenographic picture, the clinical course, and the absence of physical signs. The X-ray picture is typical, especially when the pulmonary fields are clear. There is an area of decreased density surrounded by an area of increased density. The margin is thin, dense and smooth. The area is usually ovoid and frequently varies in size from time to time. The duration may be weeks or occasionally months. The clinical course after the pneumonic lesion has cleared is entirely asymptomatic. The presence of signs or symptoms indicates secondary complication, especially otitis media. No treatment is necessary except for that of complications. No correlation has been possible with autopsy findings because of the usual benign course. Differential diagnosis must be made from lung abscess during the period of actual infection, from congenital cysts, localized pneumothorax, diaphragmatic hernia and tuberculous cavity. The mechanism involved is probably the "check valve" type of obstruction described by Jackson and Jackson. Hoover demonstrated the fact that obstruction to expiration allows the lung to become emphysematous. Van Allen demonstrated that expiratory obstruction to an entire lobe produced emphysema to that lobe, but that obstruction to smaller units did not lead to emphysema because of collateral air circulation. Therefore, obstructive emphysema is a lobar phenomenon unless something is present to interfere with collateral respiration. Collateral circulation of air is due to the combined action of pores of Kohn and to direct diffusion of air through alveolar septa. Ogawa has shown by special histological meth-

ods by which the septa are viewed in face as well as in cross section that pores actually exist. Collateral circulation is prevented by a complete septum between lobules or by inflammatory consolidation of the tissues at the border between the free and the obstructed portion of the lobe. During pneumonia conditions favorable to obstruction and to "check valve" obstruction of a bronchus are present. The bronchus is blocked by a firm mass of exudate or by viscid secretion, allowing air to flow in but not out. Eventual resolution probably occurs by slow diffusion or by removal of the initial obstruction. The length of time depends on the mechanism. Restoration to normal is eventually complete.—*Obstructive Pulmonary Emphysema Associated with Pneumonia in Childhood*, J. Leopold & E. A. Kratzman, *Am. J. Dis. Child.*, May, 1945, 69: 287.—(K. R. Boucot)

**Anemia and Hypoproteinemia in Pneumonia.**—Two cases are reported as illustration of the importance of specific supportive therapy of pneumonia in addition to specific antibacterial treatment. Two patients with protracted, bacterial pneumonia were treated with penicillin. In both patients severe and progressive anemia and hypoproteinemia were present in spite of apparent bacteriological arrest of the infection. Large amounts of whole blood and plasma were successfully used to combat the anemia and hypoproteinemia. In addition, the importance of the measures for the maintenance of optimum gas exchange in remaining functional lung tissue is stressed.—*Anemia and Hypoproteinemia Complicating Severe Protracted Pneumonia: Treatment with Penicillin—Rôle of Specific Supportive Therapy in Recovery*, S. H. Armstrong, Jr., A. C. England, Jr., C. B. Favour & I. H. Scheinberg, *J. A. M. A.*, February 10, 1945, 127: 803.—(H. Abeles)

**Etiology of Atypical Pneumonia (Part II).**—The isolation of a new virus from patients with atypical pneumonia, by inoculation of filtered suspensions of sputum or unfiltered suspensions of bacteriologically sterile human lung

tissue into the amnion of chick embryos, has been described (Part I). Passage of the virus in chick embryos was successful, but no marked increase in virulence was observed. The development of small pulmonary lesions in hamsters or cotton rats after intranasal inoculation of material from infected chick embryos was used as a means of detecting the presence of the virus. Passage of the agent in cotton rats or hamsters was found to be impracticable because of contamination with the respiratory viruses often present in these animals. In the present paper the agent propagated in chick embryos is provisionally designated as the virus of atypical pneumonia and some of its properties are described. Five strains of the virus were isolated from human material and adapted directly to the chick embryo. Two of the strains are reported in detail. The best growth of virus, as determined by the results of intranasal inoculation in hamsters and cotton rats, resulted from material incubated for seven days or more on 11-day chick embryos. The highest dilution of chick embryo suspension producing pulmonary lesions in the test animals was not over  $4 \times 10^{-3}$ . Dilutions of  $10^{-4}$  infect chick embryos. The virus was found to be unstable at room temperature and also lost activity when stored in a dry-ice refrigerator ( $-70^{\circ}\text{C}.$ ), unless the suspension was kept in sealed glass tubes. It could then be stored for as long as fourteen months without complete loss of activity. Filtration experiments showed the virus to be retained by collodion filters of 300 to 336 m $\mu$  average pore diameter, but passed filters of 366 to 400 m $\mu$  indicating a particle size of about 180 to 250 m $\mu$ . To show that the lesions produced in the test animals by the virus of atypical pneumonia were specific for this agent and not caused by respiratory viruses often present in hamsters and cotton rats, experiments in cross immunity were done. The atypical pneumonia virus produced pulmonary lesions in animals immunized to their own nonbacterial respiratory agents and, reciprocally, animals immunized with atypical pneumonia virus could still be infected with an animal respiratory virus. There resulted no

evidence of any cross-immunity.—*Studies on the Etiology of Primary Atypical Pneumonia. II. Properties of the Virus Isolated and Propagated in Chick Embryos*, M. D. Eaton, G. Meiklejohn, W. Van Herick & M. Corey, *J. Exper. Med.*, November 1, 1945, 82: 517.—(J. S. Woolley)

**Etiology of Primary Atypical Pneumonia (Part III).**—In this section detailed data on the neutralization of the virus of atypical pneumonia by serum from persons recovered from the disease are presented. The incidence of cold agglutinins and agglutinins for an indifferent streptococcus in the serum is also discussed. For the neutralization experiments inactivated human sera were mixed with normal horse serum to give various dilutions of the former. Equal parts of the active virus were then added to each tube. After standing for twenty minutes at room temperature for neutralization to take place, samples from each mixture were inoculated intranasally into hamsters and cotton rats. The highest final dilution of serum which completely prevented the appearance of macroscopic pulmonary lesions in the animals was taken as the end point. Significant increases in neutralizing antibodies were demonstrated in 42 of a total of 69 persons with a clinical diagnosis of primary atypical pneumonia. In a specially studied group of 28 patients in which a significant antibody increase was observed, the titrations showed increases of 4- to 64-fold. Eighty-three per cent of the acute phase titers were 4 or less, whereas in 86 per cent of the convalescent cases the titers were 16 or over. In the same group of 28 patients, 17 were tested for cold agglutinins and 11 of these were found positive with (maximum) titers ranging from 20 to 1280. Agglutination with the indifferent streptococcus No. 344 was observed in 11 of the 28 cases, the titers varying from 10 to 40, a titer of less than 10 being considered negative. Previously published data have indicated that in nearly all cases of primary atypical pneumonia in which streptococcal agglutinins are present, cold agglutinins are present also. This was found to be the case in the few

tests in which both forms of agglutinins were looked for. Most of the cases of atypical pneumonia included in the present study were from the Pacific Coast, but antibody increases were also found in 17 patients from the East. Geographical distribution apparently has no influence on the reactions to the disease. Patients with pneumococcal pneumonia and pneumonia caused by influenza virus type A or viruses of the psittacosis group did not have significant increases in neutralizing antibodies for the virus of atypical pneumonia. Cold agglutinins were present in 3 cases of type A influenzal pneumonia. Sera from persons with atypical pneumonia, when tested against the three most prevalent respiratory viruses isolated from cotton rats and hamsters, failed to neutralize these agents or showed no significant change in neutralization titer. It has been suggested that a toxic factor may participate in the production of pulmonary lesions in hamsters and cotton rats by the agent employed in these experiments. If this were the case the observed neutralization by human serum might be antitoxic rather than antiviral. However, the agent producing pulmonary lesions behaved more like a virus than a toxin and some evidence that the neutralization was not antitoxic was obtained in experiments in which the convalescent serum and virus were inoculated into the amnion of chick embryos with subsequent passage to hamsters or cotton rats. The data presented in this paper indicate that patients with atypical pneumonia develop in their sera an antibody which prevents the appearance of pulmonary lesions in hamsters or cotton rats inoculated with mixtures of convalescent serum and infected chick embryo tissue. There is considerable evidence that the agent producing pulmonary lesions is a virus and not a toxin.—*Studies on the Etiology of Atypical Pneumonia. III. Specific Neutralization of the Virus by Human Serum*, M. D. Eaton, W. Van Herick & G. Meiklejohn, *J. Exper. Med.*, November 1, 1945, 82: 529.—(J. S. Woolley)

**Transmission of Virus Pneumonia.**—The syndrome of atypical pneumonia may be pro-

duced by bacteria, rickettsias, fungi and viruses. In the majority of cases, however, no etiologic relationship to these known agents has been demonstrated. Experiments were undertaken to study the transmission of primary atypical pneumonia to human volunteers by means of bacteria-free filtrates. Forty-two men were segregated in individual rooms. Strict isolation technique and quarantine were observed during the eight-week course of the experiment. The inoculum consisted of sputum and throat washings obtained from experimentally produced cases of atypical pneumonia. Each man received a total inoculum of 10 cc. in three equally divided doses. The material was sprayed into the nose and throat. Three of 12 men who had received inoculum filtered through sintered glass and Seitz filters developed atypical pneumonia. Three of 12 men inoculated with untreated material developed atypical pneumonia. No case of pneumonia developed in 18 men who had received autoclaved inoculum. The appearance, development and regression of the pneumonic lesions had a striking similarity to those seen in the naturally occurring disease. Cold agglutinins were found in the serum of 5 of the 6 cases of pneumonia.—*Transmission of Primary Atypical Pneumonia to Human Volunteers, Commission on Acute Respiratory Diseases, Fort Bragg, North Carolina, J. A. M. A., January 20, 1945, 127: 146.*—(H. Ables)

**Virus Pneumonia in Infants.**—Epidemics of virus pneumonia in infants have been observed at four-year intervals in Minnesota. Premature infants were particularly susceptible. The signs consist of dyspnea, cyanosis, a white mucoid secretion on the back of the pharynx and a few râles over the involved lung portions. Numerous inclusion bodies are found in the epithelial cells obtained from the pharyngeal smear. These bodies are also found in the bronchial, bronchiolar and alveolar epithelial cells at postmortem examination. Pooled adult serum in 25 to 30 cc. doses, repeated once or twice, has been found of benefit, as well as the administration of adrenal cortical extract.

Oxygen in high concentrations, preferably by tent, is the most important supportive treatment.—*Third Epidemic of Primary Virus Pneumonitis among Infants in Minnesota, J. M. Adams, Journal-Lancet, May, 1945, 65: 192.*—(H. Marcus)

**Pulmonary Complications after Tonsillectomy.**—Lung complications following tonsillectomy are probably not due to the aspiration of infected material at the time of operation. A review of 1,020 tonsillectomies at the University Clinic of Berne, Switzerland shows that the incidence of complications was highest in operations performed under local anesthesia with the patient in the semi-upright posture. Eight postoperative complications were observed in 513 cases operated under local anesthesia. The remainder of the cases were done under ether anesthesia and no complications were observed. Blood and saliva reach the trachea of tonsillectomy patients with some regularity. It could be aspirated from the trachea in 60 to 80 per cent of patients who had general anesthesia and in 38 per cent of patients who had local anesthesia. Yet the latter group had the complications, and these are seen as frequently in the upper lobes as in the lower lobes. It is likely, therefore, that the infection reaches the lung by way of the blood-stream. Of the 8 cases observed, 6 had bronchopneumonias, one a lung abscess and one developed rapidly progressive tuberculosis. All but the latter cases did well on sulfonamide therapy. The earliest constant sign of pulmonary complication is postoperative fever starting from the second to the fifth day, and the routine measure of X-raying the febrile cases will aid in early diagnosis. The incidence of postoperative complications can be expected to rise if tonsillectomy is performed shortly after a recent tonsillitis or peritonsillar abscess.—*Über Lungenkomplikationen nach Tonsillektomie, L. Rüedi, Schweiz. med. Wchnschr., May 5, 1945, 75: 589.*—(H. Marcus)

**Acute Putrid Lung Abscess.**—One hundred and seventy-two cases of acute putrid ab-

scasses of the lung have been operated in the past sixteen years at the Mount Sinai Hospital. Acute putrid abscesses are due to aspiration of infective material. The abscess develops usually within two weeks, is usually single, and the pleura over the abscess is usually obliterated. An abscess is called acute if it is less than six weeks old. After that time usually additional lesions appear, which make the results of the operation less satisfactory. Indications for operation are: severe toxemia, unusually large abscess, invasion of the pleura, stationary small abscesses, poorly draining abscesses, sustained fever, intensely fetid sputum, diabetes. For exact localization of the abscess roentgen films should be taken in various positions; the "spot" method by Rabin is always advisable. In most cases the one-stage operation was performed, consisting "of the exposure of pleural adhesions by a limited excision of a segment of one rib (in most cases), incision through adhesions at their densest portion (at which place the bulge of the abscess will often be noted), disclosure of the abscess by aspiration, its unroofing by excision of the thin compressed shell of overlying lung, and the visualization and gauze tamponade of the abscess cavity and all its recesses." The operation is followed by immediate general improvement. There were 4 deaths in 172 operations. The bronchial fistula should be maintained until the patient is completely free of symptoms and the infiltrations have disappeared on X-ray examination, which usually takes four to eight weeks. Sometimes a plastic procedure is necessary for the closure of the cavity.—*Acute Putrid Abscess of the Lung*, H. Neuhof, *Surg., Gynec. & Obst.*, April, 1945, 80: 351.—(G. C. Leiner)

**Shut-off Pulmonary Abscess.**—The diagnosis of putrid lung abscess is frequently not made due to the absence of foul sputum. It is believed that this is caused by occlusion of the draining bronchus. This variety is called "shut-off abscess." The etiology of shut-off putrid lung abscesses is the same as that of other putrid lung abscesses. They invade the pleura more often than do abscesses with foul

sputum. They can perforate into a bronchus. The main symptoms are cough and expectoration; both may vary greatly or may be missing completely. Pain due to pleural involvement is usually present. The physical examination is not of much help in making the diagnosis. The roentgenological examination reveals persistent pulmonary infiltration, but is of no aid in differentiating between a putrid and non-putrid abscess. The diagnosis is difficult and only possible if always kept in mind. Ten cases of shut-off pulmonary abscess were seen. In 5, foul sputum was expectorated between five and sixteen weeks after the onset. In 4, foul pleural fluid was aspirated. In one case the diagnosis was made at autopsy. Operation is indicated for shut-off pulmonary abscesses.—*Putrid Pulmonary Abscess without Foul Sputum: (Shut-off Pulmonary Abscess)*, D. Stats & H. Neuhof, *Arch. Int. Med.*, September, 1945, 76: 154.—(G. C. Leiner)

**Lung Abscess**—Two hundred and forty-four cases of lung abscess seen between 1932 and 1943 are reviewed. The most common localization of the abscess was in the right lower lobe, followed in order by the left lower lobe, the right upper lobe, the left upper lobe and the right middle lobe. Forty-one abscesses developed after tonsillectomy under ether anesthesia and 27 after abdominal operation under general anesthesia. In 157 cases (65 per cent) the lung abscess followed pneumonia. Other causes were: aspiration of foreign body, subphrenic abscess, congenital cystic disease, encephalitis; in 7 cases the cause was unknown. In 8 children it was caused by aspiration of a foreign body. Cultures of sputum, of material obtained by bronchoscopic aspiration and of material from the abscess revealed pneumococci in 27 per cent of the cases, *Staphylococcus aureus* in 18 per cent, fusiform bacilli in 17 per cent, hemolytic streptococci in 14 per cent, *Micrococcus catarrhalis* in 12 per cent and spirochetes in 5 per cent. The earliest and most frequent symptom was cough. Foul sputum was present in 88.6 per cent of the patients, odorless sputum in 11.4 per cent, hemoptysis in 57.8 per cent,



chills and fever in 90 per cent and chest pain in 94 per cent. There were 154 male and 90 female patients, 208 adults and 36 children. The duration of the disease was from three weeks to nineteen years. Possible preventives of lung abscess following surgery are: (a) good care of teeth before a contemplated operation; (b) avoidance of strong sedatives before and after operation; (c) frequent aspiration of the trachea and bronchial tree by nasal catheter; (d) encouraging of patient to cough after operation; (e) early aspiration bronchoscopy in postoperative atelectasis. In acute cases, that are of less than two months' duration, surgical drainage is advised. Of 110 acute cases, 63 had surgery and 47 no treatment other than bronchoscopy; of 134 chronic cases, 101 had surgery and 33 no treatment but bronchoscopy. A lung abscess that seems not to be draining adequately through a bronchus should have external drainage. Cautery with unroofing the cavity was done in 97 cases. In cases in which the lung is adherent the operation is done in one stage. A two-stage operation was necessary in 50 per cent of the cases. Thoracotomies for empyema were done in 37 cases. Lobectomy was done in 28 cases, pneumonectomy in 2 cases; they were done when the cavity did not heal within six months after the cautery operation. Postoperative complications were: hemorrhage, spill-over, empyema, septic spread to other parts of the body. Of the 164 patients who underwent surgical treatment, 62 per cent improved, 38 per cent died. Of 80 patients treated by bronchoscopy, 61 per cent improved and 20 per cent died.—*Lung Abscess: An Analysis of 244 Cases*, A. R. Valle, Surg., Gynec. & Obst., September, 1945, 81: 278.—(G. C. Leiner)

#### Pneumonectomy in Pulmonary Suppuration.

—A 9-year-old girl was seen who had been coughing since a pertussis infection at the age of four. X-ray examination showed infiltrations in the left midlung field. The sputum was negative for tubercle bacilli. Bronchoscopy revealed no stenosis but purulent secretion from the left lower lobe bronchus. A later roentgenological examination showed atelec-

tatic foci in the upper part of the left lung field, and pneumonectomy was therefore decided upon. Ten days before the operation pneumothorax was induced on the left. Bronchoscopic aspiration was done shortly before the operation. The operation resulted in complete cure. The findings at the pathological examination of the removed lung were: bronchiectasis and fibrosis in the lower lobe; in the upper lobe, pulmonary infarcts which probably had occurred during operation.—*Suppuration broncho-pulmonaire et pneumonectomie*, J. P. Roger, J. M. Lemieux, G. L. Côté & L. Rousseau, Laval méd., June, 1945, 10: 410.—(G. C. Leiner)

**Coccidioidomycosis.**—The incubation period of primary coccidioidomycosis varies from eight to twenty-one days. An acute, a subacute or chronic active and an arrested or healed stage can be distinguished in the course of the disease. The acute stage is characterized by respiratory symptoms, pleuritic pain, cough, hemoptysis in some cases. Chills and fever are frequent, varying from a high temperature for a few days to a low grade temperature for weeks. Sore throat is a frequent complaint. A fine macular generalized rash within the first few days is described. Physical examination may reveal signs of acute bronchitis, pneumonia or pleurisy. Within eight to fourteen days erythema nodosum and/or erythema multiforme occurs in 5 to 20 per cent of all patients. At the same time arthritic pains are observed in 30 per cent. The sedimentation rate is elevated, the leucocyte count is not significant, eosinophilia is often present. The coccidioidin skin test is positive. This initial acute infection occurs in the endemic area. The subacute or chronic active stage may be considered as that period following the disappearance of acute manifestations in which, however, there is evidence of activity as manifested by changing pulmonary lesions in chest roentgenograms. Weight loss and subfebrile temperatures are usually present. The arrested or healed stage is designated as any time following disappearance of active infection when clinically silent lesions are



demonstrated radiologically. The chest film shows a group of circumscribed lesions, nodular in character. There is a history of residence in an endemic area. The coccidioidin skin test is positive. Precipitin test and complement fixation test may be helpful. The diagnosis is established by demonstration of the fungus by culture or guinea pig inoculation. The roentgenological findings during the acute stage are hilar adenopathy, patchy parenchymal infiltrations or pleural effusion. Thin-walled cavities may develop. Late cases may show linear fibrotic markings, thickened pleura, atypical parenchymal lesions or nodular lesions. The single or multiple nodular pulmonary lesions may be confused with tuberculous or metastatic lesions. The fungous lesions usually show serration of the edges. The prognosis is good. Four cases of coccidioidomycosis are reported, one was associated with tuberculosis. Attention is drawn to the problem of recognition of coccidioidomycosis in children returning from endemic areas in the Western states, where they have been sent to obtain the advantages of a dry climate in the treatment of respiratory diseases.—*Primary Coccidioidomycosis: A Possible Pediatric Problem*, R. H. Kunstaster & R. C. Pendergrass, J. A. M. A., March 17, 1945, 127: 624.—(H. Abeles)

**Pulmonary Aspergillosis.**—This is a case report of acute pulmonary aspergillosis. The patient was a 59 year old man who was admitted with the diagnosis of lobar pneumonia. Sulfathiazole was ineffective and the patient rapidly got worse and death seemed imminent. Sputum culture showed pure culture of *Aspergillus fumigatus*. Increasing doses of potassium iodide were then given, starting with 6 g. Improvement was noted practically immediately, and the dosage was increased to 45 g. daily. Recovery was rapid and uneventful and the patient remained well when seen two months later.—*Acute Pulmonary Mycosis*, Elizabeth Delikat, Lancet, September 22, 1945, 249: 370.—(H. Marcus)

**Megamycetoma.**—This is the second such case reported in the world literature. A 24 year old woman had periodical hemoptyses for seven years nearly always during the menstrual periods. Otherwise she was normal. During a pregnancy she had an abundant hemoptysis. Physical examination at that time was negative. An X-ray film of the chest showed an ellipsoid shadow in the left pulmonary field. Search for tubercle bacillus was negative. Tuberculin test was positive. A fungus was recovered from the sputum. Skin tests with trichophyton were positive. The diagnosis of megamycetoma, tumor form, was made. Iodides and later arsenicals were given. Radiographically and clinically the patient improved and up to ten months after the treatment was started she did not have any more hemoptyses.—*Micosis pulmonar a forma tumoral: Megamicetoma*, R. Denis, A. P. Huidlass & J. A. Marti, Bol. d. Hosp. F. Santojanni, 1945, 1: 64.—(P. B. Franca)

**Chronic Obliterative Bronchiolitis.**—A disseminated fibrosis of the type that one finds in silicosis is occasionally found in chronic purulent obliterative bronchiolitis. This disease is caused by chronic irritation with a corrosive agent. The authors present the case of a 57 year old male who worked in a foundry for twenty-two years, with duties involving sanding of metals. During the last two years there were progressive dyspnea, cyanosis, mucopurulent expectoration, anorexia, loss of weight and hemoptysis. On examination there were mild dyspnea at rest and bilateral sibilant râles. X-ray film was typical of silicosis. Analysis of the dust inhaled showed 10 to 15 per cent silicon dioxide, and iron. On autopsy the main findings were in the lungs, with bronchiectasis, purulent bronchiolitis, and pulmonary sclerosis. There was no evidence of tuberculosis or silicosis.—*Contribution à l'étude radiologique et clinique de la bronchiolite oblitérante purulente chronique accompagnée d'une sclérose prononcée du parenchyme pulmonaire*, G. Voluter & F. Sciclounoff, Schweiz. med. Wchnschr., June 2, 1945, 75: 484.—(J. Gerstein)

# STREPTOMYCIN IN TREATMENT OF CLINICAL TUBERCULOSIS<sup>1</sup>

H. CORWIN HINSHAW,<sup>2</sup> WILLIAM H. FELDMAN<sup>3</sup> AND KARL H. PFUETZE<sup>4</sup>

Although efforts to develop a clinically practicable chemotherapeutic or antibiotic aid for tuberculosis have long been exerted, there was little optimism about this until success was attained in treatment of other bacterial infections with such drugs as sulfonamides and penicillin. These drugs, however, did not prove to be of value in treatment of tuberculosis.

The search for a chemical or antibiotic remedy for tuberculosis has been handicapped by the fact that the usual experimental methods employed in study of chemotherapy of acute diseases have not proved to be of practical value. It has been necessary to employ a much slower and more difficult type of experimental procedure to reveal the antituberculosis potentialities of such drugs as those of the sulfone series and more recently streptomycin. The procedures which we have employed for the past seven years have been adequately described in previous communications (1, 2) and have permitted a roughly quantitative comparison of the potentialities of drugs in experimental tuberculosis. When such methods were employed in a study of streptomycin early in 1944, it was possible to recognize this as a substance of unusual promise (3, 4). Although streptomycin was announced only two and a half years ago (5), much of the necessary data have been assembled to indicate that its production and use are commercially and clinically practicable. In view of the fact that streptomycin will soon be available in increasing quantities, it seems advisable to record our clinical experiences with this drug in treatment of tuberculosis. Our clinical study has been under way for over one and a half years.<sup>5</sup> Preliminary clinical reports have previously been made (6-8) after necessary pharmacological studies (9).

## MILIARY TUBERCULOSIS AND TUBERCULOUS MENINGITIS

These rapidly progressive and highly fatal forms of tuberculosis were chosen for early study to obtain information on toxicity and methods of administration of streptomycin and with the belief that any consistent modification of the clinical course of such diseases would be of great therapeutic significance.

Ten patients who had generalized hematogenous tuberculosis with or without

<sup>1</sup> Presented before the Medical Section at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 12, 1946.

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<sup>5</sup> The streptomycin employed in these studies was derived from several sources. The larger quantity was supplied by Merck & Company and by the Abbott Laboratories. Streptomycin was also supplied by the Upjohn Company, Eli Lilly and Company and, since March 1, 1946, all supplies have been obtained through the Committee on Chemotherapeutics and Other Agents of the National Research Council, Dr. Chester S. Keefer, Chairman.

meningitis have been treated with streptomycin and the results have been sufficiently consistent to permit some conclusions to be drawn. Four patients of this group are still living, having survived for periods of from three to six months following the proved diagnosis of acute tuberculous meningitis. In each of these 4 patients persistent clinical findings indicate the possibility of residual infection, and the long-term prognosis appears to be uncertain. However, in each case suppression of the disease process has occurred for a long period with consistent clinical improvement which can be attributed to the treatment with streptomycin. Each of these 4 surviving patients presented the classical syndrome of acute tuberculous meningitis with high fever, stupor, nuchal rigidity and the usual findings on examination of the cerebrospinal fluid, including the demonstration of tubercle bacilli. Clinical improvement with return of normal consciousness, improvement of neurological signs and cessation of such symptoms as headache occurred within one to three weeks after treatment was begun. Fever declined rapidly during the first and second weeks, then more slowly and did not reach the normal level until after several weeks of treatment. Persistent abnormal findings in the cerebrospinal fluid have been noted in 3 of the 4 cases, but it is no longer possible to find tubercle bacilli in the spinal fluid of 3 of these patients, either by cultural methods or by inoculation of guinea pigs. None of these patients can as yet be regarded as cured but evidence is fully sufficient to conclude that the clinical course of the disease has been altered in a favorable manner, at least temporarily.

It may be significant that these 4 patients are the only ones in whom we employed streptomycin intrathecally for prolonged periods of time (two to four weeks). In these cases lumbar or cisternal puncture with injection of 100 to 200 mg. was carried out daily. In addition, intramuscular injections of 1.2 to 3.6 g. were given daily for periods of from three to six months. Presentation of detailed reports of these cases will be postponed until the eventual outcome is more clearly evident.

The remaining 6 patients in this group failed to survive despite parenteral treatment with streptomycin in large doses. Data on these cases will be published soon in collaboration with Dr. Baggenstoss of the Section on Pathologic Anatomy and will tend further to substantiate the conclusion that streptomycin modified the clinical course and the pathological findings in cases of acute hematogenous disseminated tuberculosis, even in those instances in which the patient did not survive.

In evaluating these results it should be recalled that generalized hematogenous infections caused by organisms susceptible to the action of such drugs as penicillin still have a high mortality rate despite treatment. This is especially true if the central nervous system is involved (for example, pneumococcic meningitis).

#### PULMONARY TUBERCULOSIS

Pulmonary tuberculosis is such a prevalent and disabling disease that the therapeutic potentiality of any antituberculosis substance becomes a problem of greatest interest and importance. Any drug of low toxicity which has definite

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few weeks of treatment. Subjective factors were discounted because of the well known effects of morale on symptomatic improvement in tuberculosis.

Serial roentgenograms taken at frequent intervals (every one to four weeks) demonstrated improvement of fresh exudative lesions within a few weeks after treatment was begun. This was followed frequently by progressive reduction in size of thin-walled cavities, which eventually disappeared in most instances. Occasionally dense shadows which were thought to represent areas of caseation tended to coalesce, soften and excavate. The roentgenological appearance of thick-walled cavities of long standing frequently did not change and lesions which were predominantly fibrous or fibrocaceous were often unaffected by treatment during the period of observation. These mechanical factors appeared to act as handicaps to the healing process exactly as would be predicted on theoretical grounds.

Sputum has not been regarded as negative for tubercle bacilli unless aspirated gastric contents were repeatedly negative either on inoculation of guinea pigs or culture. Reversal of sputum from positive to negative occurred in most of the cases in this small series in which there were no chronic thick-walled cavities. The permanence of such a change in the sputum remains to be demonstrated and we would prefer to postpone more detailed reports until observation is complete. Old cavernous fibrocaceous lesions appeared to offer a definite barrier to arrest of the disease and the continued presence of tubercle bacilli in the sputum was usually noted in such cases. Eventually cultures of the sputum in cases of such lesions yielded tubercle bacilli which were found to be resistant to the effects of streptomycin *in vitro* (10). The clinical implications of acquired drug-fastness by tubercle bacilli *in vivo* have not been fully explored but observations and theoretical considerations are discussed in a later paragraph.

The dosage of streptomycin employed in treatment of pulmonary tuberculosis has been lower than that utilized in treatment of tuberculous meningitis and miliary tuberculosis. We have come to regard the minimal daily dose as 1 g. (1,000,000 S units) and the ideal dose somewhat higher, 1.5 to 2 g. daily for patients of average weight. Doses of 3 to 10 g. daily have been employed occasionally but these quantities appear frequently to produce toxic reactions. The duration of treatment has varied from six weeks to six months. Some of the 24 patients with pulmonary tuberculosis were treated during the earliest developmental phases of streptomycin production; hence dosage was frequently dictated by limitations of supply. At other times dosage was restricted by appearance of undesirable side reactions, prior to present-day accomplishments of the manufacturers in purification of the drug.

The periods of observation have been inadequate to determine the effect of streptomycin therapy on the eventual prognosis in some of the patients with far advanced, destructive tuberculosis under study. In some instances it appears improbable that the accomplishments have been more than palliative. Other patients with inoperable pulmonary tuberculosis have apparently improved sufficiently to undergo such operations as thoracoplasty and pulmonary resection. In cases without thick-walled cavities and other mechanical obstacles to healing,

the disease process appears to have been altered in a favorable manner within a few months to a state of inactivity which may or may not be sustained.

Two of the 24 patients have died. These patients were in the terminal phases of the disease when treatment was started; one survived for two months and the other for eight months. The latter died two months after discontinuation of a six-month course of treatment.

The tendency to reactivation of tuberculous infection on cessation of treatment previously described (6, 7) does not seem to be as great in cases of pulmonary tuberculosis as in cases of some types of extrapulmonary tuberculosis. Furthermore, this tendency to recurrence is less frequent in patients with pulmonary tuberculosis when treatment is continued for a long time (three to six months) and large doses are employed (2 to 3 g. per day) than when smaller doses are given for briefer periods. Fortunately, reasonably dependable and durable natural healing mechanisms are available in pulmonary tuberculosis which are inadequate in some types of extrapulmonary tuberculosis, such as tuberculous meningitis, renal and cutaneous tuberculosis. When the restraining influence of the drug is withdrawn, either by cessation of treatment or by development of drug resistance in the tubercle bacilli, the patient is again dependent on these natural defense factors for consolidation of any gains achieved. These considerations, if further study proves them correct, will have a great influence on selection of cases for treatment with streptomycin.

#### ULCERATING TUBERCULOUS LESIONS OF RESPIRATORY PASSAGES

Lesions of the larger bronchi, trachea, larynx and hypopharynx can be observed directly or by endoscopic methods and frequently are resistant to conventional methods of treatment. These types of tuberculosis are grouped together because a similar method of treatment was employed. This method consisted of direct application of the drug by means of nebulized aerosol, as well as by intramuscular injections. Treatment was given in 3 cases of previously progressive ulcerative tracheobronchitis, 2 of ulcerating lesions of the hypopharynx and larynx with extremely severe dysphagia and in one case of tuberculous laryngitis previously reported (8). The response to treatment was prompt and rapid in each of these 6 patients. Marked objective improvement was obvious within two to four weeks and symptomatic improvement was noted within several days. Healing of visible lesions has been complete in each instance and no recurrences have been observed, although several months have elapsed since treatment was discontinued. Although this series of 6 patients is small, it indicates the desirability of further exploring the possibilities of streptomycin therapy in such types of tuberculosis.

#### OTHER EXTRAPULMONARY TYPES OF TUBERCULOSIS

The study of tuberculous lesions involving the various structures of the human body has been facilitated by collaboration with physicians interested in such specialities as pathology, urology, dermatology, laryngology, ophthalmology, neurology, surgery, pediatrics, orthopedics and so forth. We recognize that

physicians in these fields are best qualified to analyze some of the therapeutic results achieved by streptomycin in various types of extrapulmonary tuberculosis. More detailed case reports will be made subsequently in collaboration with our associates in these special fields, and the present communication will be limited to a general discussion of the clinical trends observed.

*Draining sinuses of tuberculous origin:* Patients with external fistulae were chosen for treatment because of the ease with which such lesions could be observed and photographic records made. A total of 8 such patients were treated with streptomycin. In each case it was first ascertained that the disease had been present for at least several months and that no spontaneous tendency to healing had been observed in these lesions. Five of these had cervical and axillary tuberculous lymphadenitis with external fistulae, 2 had tuberculosis involving the chest wall, and one had persistent abdominal sinuses following operation for tuberculous peritonitis.

In each of the 8 cases purulent exudate ceased within three to eight weeks of the time treatment with streptomycin was begun. In 5 cases the sinuses subsequently healed completely. In 3 patients with tuberculous adenitis healing was incomplete when treatment was discontinued and purulent drainage promptly recurred, possibly because of inadequate treatment. The lowest dosages and the shortest periods of treatment were used in these 3 cases. This exacerbation was apparently due to residual infection in deeper layers of tissue, and it is uncertain whether more intensive and prolonged treatment would have yielded superior results. In 2 of the 3 cases of recurrent sinuses we have had the opportunity of administering second courses of treatment and responses were similar to those that followed the first courses of treatment. Evidently the causative organisms had not become clinically drug-fast; unfortunately, *in vitro* studies were not made on bacilli isolated from these patients.

The 2 patients with tuberculous sinuses of the chest wall are included in the 5 in whom complete healing occurred and has been maintained for more than six months following discontinuation of treatment. The patient with abdominal sinuses, persisting after operation for tuberculous peritonitis, also had tuberculous meningitis which is now quiescent after six months of continuous treatment. His abdominal sinuses closed during the first four weeks of treatment and now appear to be completely healed.

*Renal tuberculosis:* The experiences of our research group in treatment of 14 cases of renal tuberculosis with streptomycin will be reported at an early date with our collaborators in the field of urology. Treatment with streptomycin was given only to patients in whom surgical treatment was impracticable, especially in cases of bilateral renal tuberculosis and in those of tuberculosis in a solitary residual kidney, the other kidney having previously been removed because of tuberculosis. Although the early response to treatment frequently is promising under these conditions, our attitude has become more pessimistic with passage of time because of the tendency of tuberculous bacilluria to recur, even when other symptoms have not recurred. Clinical and pathological studies in renal tuberculosis have long indicated that the human kidney strangely lacks the

power to heal lesions of tuberculosis. Evidence is accumulating to suggest that streptomycin is primarily of palliative value in tuberculosis of the urinary tract and has more effect on tuberculosis cystitis than on infection in the kidney.

*Miscellaneous types of extrapulmonary tuberculosis:* Table 1 summarizes our experience with treatment of a wide variety of lesions of tuberculosis. The number of patients treated in several categories is very small and inadequate

TABLE 1  
*Treatment of tuberculosis with streptomycin*

TYPE OF TUBERCULOSIS	NUMBER OF CASES	APPARENT FAVORABLE RESPONSE	REMARKS
Miliary (without meningitis)	3	3	All patients died following temporary improvement. Roentgenological and pathological evidence of healing trend
Meningitis	7	6	4 patients living and improved; 2 died following temporary improvement; 1 patient died in five days, no improvement
Pulmonary	24	19	No lesions extended during treatment; 3 patients unimproved; 2 deaths (treatment started in terminal phase of disease)
Ulcerating lesion of hypopharynx, larynx, trachea and large bronchi	6	6	Aerosol and parenteral therapy combined
Cutaneous fistulae of neck, thorax and abdomen	8	5	Marked tendency to recurrence especially if treatment period is brief
Empyema	7	1	Intrapleural treatment alone unsuccessful
Kidneys and bladder	14	8	Palliative effects frequently noted. Marked tendency to recurrence
Lupus	3	1	Tendency to recurrence noted
Bones and joints	4	2	No spectacular results noted
Peritonitis	3	2	Results difficult to evaluate
Total cases excluding duplicates	75*		

\* 4 patients had lesions of more than one type.

as yet to indicate the therapeutic possibilities of streptomycin for the lesions tabulated.

In all 7 cases tuberculous empyema was treated by intrapleural administration of streptomycin, and in 3 cases this was combined with intramuscular injection. In only one case was improvement observed in excess of that which should be anticipated as a result of the pleural lavage which was carried out.

The cases of lupus tabulated are included in a forthcoming publication written in collaboration with Drs. O'Leary and Ceder of the Section on Dermatology of the Mayo Clinic. Two had *lupus vulgaris* and one *lupus miliaris disseminatus*.

Tuberculous lesions of bones and joints should receive much more study, but the outlook does not appear favorable for any type of drug therapy to be effective



in a spectacular manner in view of the destructive character of such lesions of tuberculosis. Streptomycin eventually might prove to be a useful adjunct to surgical treatment.

#### DRUG-FASTNESS

It has been clearly established that *Mycobacterium tuberculosis* is capable of acquiring *in vivo* a resistance to the bacteriostatic action of streptomycin (10). Undoubtedly strains of tubercle bacilli vary in this respect and the effects of varying dosage and continuity of administration are not known.

Clinical observations are sufficient to make it appear that patients continue to respond to streptomycin therapy for an adequately long period to permit recognizable therapeutic accomplishments. Evidence is accumulating to indicate that the duration of effective administration continues for at least several months. We have mentioned elsewhere the tendency for some types of tuberculosis to recur a few weeks after a short course of treatment had been completed. In several such instances we have had the opportunity of treating recurrent disease and have noted what appeared to be prompt response to the second course of treatment with streptomycin. In at least 2 cases in which recurrence of pulmonary tuberculosis followed six months of treatment, however, the disease did not appear to come under control when a second course was given. In a third case in which a second course was given for a similar period, the clinical response was apparently obtained.

It is obvious from the foregoing that much more detailed studies are necessary and that such studies might yield information of great significance with regard to the mechanism of action of these drugs. However, the real test in an individual case is the clinical test, and so long as objective improvement is demonstrable as an apparent result of the treatment, the indication for continuation of treatment is clear. It is true that the natural defense mechanisms of the human body must eventually assume responsibility for control of the infection, but we have no measure of this capacity.

The mechanism of acquired drug resistance is not understood, but experience with other infectious diseases amenable to streptomycin has suggested that resistance to the effects of streptomycin is rather easily accomplished by several species of microorganisms. This would appear to be a serious shortcoming of the drug and not a peculiar property of *Mycobacterium tuberculosis*. As a matter of fact, tubercle bacilli acquire resistance to drugs *in vivo* much more slowly than other microorganisms with which we are familiar. This slow development is due perhaps to the slow rate of multiplication of the tubercle bacillus. If our apprehension with regard to the limitations of streptomycin therapy imposed by this factor is fully realized, it will make the search for other remedies all the more urgent.

#### DOSAGE AND METHODS OF ADMINISTRATION

The patients in this series usually have received streptomycin by intramuscular or deep subcutaneous injections; the total dose per twenty-four hours varied

from 1 to 3 g. in most instances. In an effort to maintain constantly effective levels in the blood, the injections were made at intervals of three to six hours, day and night. The duration of treatment varied widely and was often dependent on availability of supplies, but we have come to regard two months as a minimal period of continuous treatment, and six months of treatment frequently appears to be desirable in severe types of tuberculous infection. It is immediately clear that treatment with streptomycin involves great expense for purchase of the drug, much nursing and medical care and courageous forbearance on the part of the patient who receives these hundreds of injections.

#### TOXICITY

The toxemic reactions to treatment with streptomycin have been described in previous articles (9, 11, 12). As manufacturing processes have improved, it has become increasingly evident that impurities accounted for the histamine reactions, the severe irritation at the site of injection, most of the cutaneous reactions and at least some of the signs of renal irritation. Even highly purified preparations of streptomycin continue to produce the unique effects on the vestibular apparatus which we mentioned in our earliest clinical reports (6, 7) and which will be considered in greater detail in an early publication (12). These reactions produce sufficient discomfort to justify denying streptomycin to patients who are likely to recover satisfactorily on the conventional therapeutic regimen. However, the actual potentialities for serious harm are so small that treatment with streptomycin if available should not be withheld in cases in which the prognosis is grave.

Actual overdosage may produce in occasional susceptible persons at least temporary deafness and probably reversible renal damage. It is not known whether these effects are due to streptomycin or impurities. We have also described acquired sensitivity to streptomycin preparations (6) which is observed only rarely.

#### COMMENT

Some types of tuberculous lesions of man tend to heal spontaneously and sometimes at an unexpectedly rapid rate. This is especially true of fresh exudative lesions of pulmonary tuberculosis and has led to serious errors of judgment with respect to alleged remedies. Claims which are based solely on evidence of healing of such lesions must be viewed with skepticism and carefully balanced control studies should be required before such claims are accepted. Controlled observations are most difficult but highly desirable and it is hoped that such studies may yet be accomplished with streptomycin. However, the evidence for the therapeutic effect of streptomycin, presented herein, is based on study of several types of tuberculous disease, including some of the most progressive and fatal forms.

When judgment is being passed on a therapeutic procedure for tuberculosis, it is logical to include the information obtainable from laboratory experimentation in so far as such data are applicable to tuberculosis in man. Well con-

trolled observations on experimental tuberculosis of guinea pigs (4) and mice (13) have established the ability of streptomycin to combat effectively the disease process, despite difficult experimental conditions. Streptomycin is the first drug which we have employed clinically for tuberculosis which has this ability and which is also so well tolerated by human beings that doses comparable to those received by the experimental guinea pigs on the basis of body weight may be administered. Evidence is accumulating to indicate that the clinical, roentgenographic and pathological results are those that would be anticipated from experience with experimental animals. Observations on experimental animals also may yield clues as to dosage and duration of treatment of patients. In this connection we recall that in the most extensive study (4) the guinea pigs were treated continuously for five and a half months with apparent eradication of the infection from approximately a third of the animals and arrest of the disease in the remaining two-thirds. This has indicated the need for prolonged and sustained treatment of tuberculosis of human beings, especially in those forms of tuberculosis in man which tend to recur. Clinical experience has again borne out this fact which was predicted on the basis of animal experimentation.

Long study will be required to determine the optimal dosage of streptomycin and duration of treatment in various clinical situations. The types of tuberculosis which may be benefited, when these benefits are merely palliative and when permanent gains may be anticipated remain to be fully determined. The present project is not adequate in scope, at this time, to answer fully these and other important questions which must eventually be answered. Our studies have indicated that streptomycin has impressive therapeutic possibilities. If these findings are confirmed, it would seem important to have demonstrated that clinical tuberculosis is amenable to the drug therapy approach, a point of view quite at variance with the concepts of a few years ago.

An important principle of scientific research calls for reservations in accepting a new principle until the results of the original group of investigators have been fully confirmed by other research workers, using similar methods of study. Adherence to this principle will guard against errors in method and errors in interpretation. In antibiotic treatment of tuberculosis, we believe that caution should be exercised by physicians and patients in their acceptance of the principles outlined in the present communication until such time as others have confirmed or disproved the results and interpretations recorded.

#### SUMMARY

Streptomycin is a therapeutic antibiotic substance highly effective against tuberculosis of experimental animals and is of low toxicity for man. We have used this drug in treatment of a variety of tuberculous lesions in a series of 75 patients. The results observed are consistent with the hypothesis that streptomycin exerts a suppressive effect on the progress of tuberculous infection in man. Limitations to the intensity of the antibacterial activity and possibly to its duration have been demonstrated.

Streptomycin may represent the first clinically feasible antibiotic remedy for

tuberculosis, but at this time it cannot be recommended as a substitute for accepted therapeutic procedures, the efficacy of which have been proved by long experience.

#### SUMARIO

La estreptomicina es un antibiótico dotado terapéuticamente de mucha eficacia contra la tuberculosis de los animales de experimentación y de poca toxicidad para el hombre. Esta droga fué empleada por los A. A. en el tratamiento de distintas lesiones tuberculosas en una serie de 75 enfermos. El resultado observado es compatible con la hipótesis de que la estreptomicina ejerce efecto supresor sobre la evolución de la infección tuberculosa en el hombre. También se observaron ciertas limitaciones de la intensidad, y posiblemente de la duración, de su actividad antibacteriana.

La estreptomicina acaso represente el primer remedio antibiótico clínicamente aplicable a la tuberculosis, pero por ahora no puede recomendarse como sustituto de las terapéuticas aceptadas y de eficacia comprobada por larga observación.

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## DISCUSSION

Mr. William Steenken, Jr. and Mr. Emanuel Wolinsky, Trudeau, New York: I wish to take this opportunity to congratulate Doctor Feldman and Doctor Hinshaw on their excellent paper, the subject of which is of vital interest to us all. It is of especial interest to my collaborators and myself since we too have had the opportunity to study the action of streptomycin in the test tube and in the animal body as well.

I agree with Doctor Feldman and Doctor Hinshaw that streptomycin is the least toxic and the most effective chemotherapeutic agent that we have so far tested against a well established and progressive tuberculosis in guinea pigs. Those of us who have had many years' experience in the study of the biology of the tubercle bacillus and the response of the animal body to the various types of tubercle bacilli are amazed at what appear to be the curative properties of streptomycin.

The results of our *in vitro* studies show that streptomycin in concentrations of 0.05 microgram per cc. exerts a certain degree of inhibition upon the growth of H37 Rv microorganisms, that 0.2 microgram produces a more marked inhibition and that 0.4 microgram inhibits completely when growth recording is made between the sixteenth and twenty-first day in media of pH 7.1 to 7.4. Approximately the same amount of streptomycin was necessary to inhibit the H37 Rv whether we used Dubos medium or surface and deep seated growth in Proskauer and Beck synthetic medium.

*In vivo*: Eight guinea pigs were vaccinated subcutaneously with 2.5 mg. dry weight of living H37 Ra microorganisms on three alternate days. Ten weeks later, these 8 vaccinated animals, plus an additional 32 normal ones, were injected subcutaneously in the groin with 0.21 mg. dry weight of the H37 Rv.

Forty-seven days later, all animals reacted strongly to a skin test with 5 per cent OT. Sample killings were made at this time, and the non-vaccinated animals had far advanced disease of the lungs, livers, spleens and lymph nodes, with ulcers at the site of inoculation. On the forty-ninth day, treatment with streptomycin was begun. Four of the vaccinated and 14 of the non-vaccinated guinea pigs were given 4,000 units subcutaneously every four hours, or a total of 24,000 units per day (31,500 units per kg. per day). This was continued for twenty days, after which the dose was reduced to 16,000 units a day, 4,000 units every four hours during the day only.

At the end of forty days, the vaccinated treated, as well as half of the non-vaccinated treated animals were taken off treatment. Treatment was continued for the remaining half of the non-vaccinated animals for a total of 125 days, at which time the experiment was terminated.

*Results*: Of the 12 non-vaccinated control animals, all died of tuberculosis, with an average rating<sup>7</sup> of 15. The first died sixty-nine days after infection, the last 140 days after, with an average length of life of 103 days. All the animals in the remaining four groups were alive at the end of 175 days. Of the vaccinated controls, 4 animals were killed after 175 days; they had an average rating of 10. The vaccinated animals which were treated forty days and were off treatment eighty-eight days (4 animals) were killed after 175 days and had an average rating of 3. The non-vaccinated animals treated forty days and off treatment eighty-eight days (7 animals) were killed after 175 days and

<sup>7</sup> For the purpose of record and comparison, the involvement of the liver, spleen, lungs and lymph nodes was noted and individually assigned values were given proportionate to the extent and severity of the tuberculosis. The minimum rating of 4 for any organ was used to indicate wide-spread caseous disease diagnosed by gross inspection. The maximum value of 16 for the animal as a whole signified far advanced, generalized tuberculosis.

had an average rating of 11. The non-vaccinated animals treated continuously for 125 days (7 animals) were killed after 175 days and had an average rating of 1.

The skin sensitivity waned in those animals that were treated for 125 days, until some of the animals were almost negative when they were skin tested with 0.1 cc. of 5 per cent OT.

There was a marked loss of weight during the first ten days of treatment that might be attributed to a rapid breaking down of the organisms, thus causing a tuberculinization of the animal, since the treated animals gained weight from then on until they were killed.

Ulcers at the site of inoculation all healed completely within the first twenty days of intensive treatment, while in the control groups these ulcers, when present, progressed steadily.

Streptomycin serum levels after two weeks of treatment, with blood withdrawn four hours after the last dose, were 3.0 to 7.5 units per cc. On the last day of the experiment, the one-hour serum levels were 7.0 to 13.0 units per cc. and the four-hour levels were 1.2 to 1.8 units per cc.

For studying the effect of streptomycin on the growth of tubercle bacilli, the method utilizing the liquid medium of Dubos was found to be the most satisfactory.

Various exudates and tissue extracts, including tuberculous guinea pig livers, spleens and lungs, ascitic fluid, serous and purulent pleural fluids, were tested for antagonism to, or inhibition of, the action of streptomycin. Streptomycin was not appreciably affected by any of these. It was also determined that high concentrations of streptomycin did not inactivate tuberculin.

# THE EFFECT OF WATER SOLUBLE LIPIDS ON THE GROWTH AND BIOLOGICAL PROPERTIES OF TUBERCLE BACILLI<sup>1,2</sup>

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AND CYNTHIA PIERCE

The slow and peculiar mode of growth of tubercle bacilli in the classical bacteriological media often hinders or prevents the application of bacteriological and immuno-chemical techniques to the study of tuberculous infection. We have shown elsewhere that the addition of water soluble lipids and of serum albumin to simple synthetic media allows fairly rapid and diffuse growth of virulent tubercle bacilli and may thus facilitate certain aspects of the experimental study of tuberculosis (Dubos (1), Dubos and Davis (2)). We shall briefly discuss in the present paper some of the factors which affect the initiation of growth of small inocula of these organisms and outline the biological characteristics of the cultures growing diffusely in liquid media containing these water soluble lipids.

## SUBMERGED AND DIFFUSE GROWTH OF TUBERCLE BACILLI IN LIQUID MEDIA

A number of water soluble esters of long chain fatty acids have been found to facilitate the submerged and diffuse growth of avian, bovine and human tubercle bacilli, as well as of other mycobacteria, in a variety of synthetic and complex liquid media. This effect can be readily observed with a synthetic ester of oleic acid, commercially available under the name of "Tween 80".<sup>4</sup> Tween 80 is a polyoxethylene derivative of sorbitan monooleate which is completely soluble in water and heat stable. Diffuse growth of mycobacteria can be obtained by incorporating this substance in a medium of the following composition.

Asparagin or hydrolysate of casein	1 gram
Na <sub>2</sub> HPO <sub>4</sub> ·12H <sub>2</sub> O	6.3 gram
KH <sub>2</sub> PO <sub>4</sub>	1.0 gram
Na citrate·2H <sub>2</sub> O	1.5 gram
Dissolve, then add	
Ferric ammonium citrate	0.1 gram
MgSO <sub>4</sub> ·7H <sub>2</sub> O	0.6 gram
Tween 80	0.5 gram
Distilled water to 1000.0 ml.	

The medium can be autoclaved; its final reaction should be pH 6.8 to 7.0.

<sup>1</sup> From the Laboratories of the Rockefeller Institute for Medical Research, New York, New York.

<sup>2</sup> Presented, in part, before the Medical Section at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 11, 1946.

<sup>3</sup> Senior Assistant Surgeon, Tuberculosis Control Division, United States Public Health Service.

<sup>4</sup> This product is manufactured by the Atlas Powder Company, Wilmington, Delaware, which generously contributed material and advice to this study.

Following inoculation of 5 ml. of this medium with 0.01 mg. of tubercle bacilli, macroscopic evidence of growth can be obtained after two days incubation at 37° C. with avian strains and after three to four days with human strains. An abundant and diffuse growth, consisting of individual cells and of microscopic clumps, is usually obtained after five to seven days incubation.

Although the medium described above is thus capable of supporting rapid growth of tubercle bacilli, it usually does not permit the development of very small inocula of the same organisms. This result can be obtained, however, by adding to the basal medium 0.1 to 0.2 per cent of serum albumin (introduced aseptically in the form of a filtered, sterile solution). Albumin prepared from the serum of several animal species appears satisfactory for this purpose; we have found it convenient to use bovine albumin serum fraction V which is available commercially as a standardized desiccated product.<sup>5</sup> In the presence of this protein, submerged growth can be obtained within ten to fourteen days following inoculation of 5 ml. of medium with  $10^{-8}$  mg. bacilli. The addition of glycerol to the medium often inhibits the multiplication of small inocula and never increases the initial rate of growth. Small amounts of glucose increase the yield of bacilli, but do not affect appreciably the initial rate of multiplication.

It is not within the scope of this paper to present the detailed experimental data which have led to the development of the cultural method utilized in the present studies. It may be worth while, however, to present briefly the following hypothesis which appears to account for some of our findings.

The water soluble ester of oleic acid, designated as Tween 80, is a surface active substance characterized by the possession of both lipophilic properties (determined by the long aliphatic chains of the fatty acid) and hydrophilic properties (supplied by the oxygen-containing groups of the polyhydric alcohols and of the ethylene oxide chains). Tween 80 is readily adsorbed on the hydrophobic surface of the tubercle bacillus and its wetting effect permits diffuse distribution of the organism in the aqueous medium. It is also likely that wetting of the bacterial surface facilitates exchanges between the organism and the environment and thus increases the rate of growth.

We have established that the addition of certain long chain fatty acids—oleic acid for example—to bacteriological media can, under well defined conditions, markedly increase the amount of growth yielded by certain strains of tubercle bacilli (avian strains in particular). Since these organisms contain a lipase which can hydrolyze Tween 80 and release from it the free fatty acid, the former substance acts not only as a wetting agent, but also contributes positively to the nutrition of the bacterial cell by supplying the fatty acid in a readily available form.

Although oleic acid can be utilized by tubercle bacilli (certain strains at least), it also exerts a powerful toxic effect on these same organisms. This fact probably accounts for the failure of growth of small inocula in the presence of Tween 80, since the commercial preparations of this substance contain small amounts of unreacted, free oleic acid (approximately 0.3 per cent). Media prepared with

<sup>5</sup> This product can be obtained from the Armour Laboratories, Chicago, Illinois.



purified Tween 80, rendered essentially free of uncombined oleic acid, often permit growth of inocula containing only a few living bacilli. Serum albumin can neutralize the toxic effect of oleic acid (and therefore of Tween 80) without interfering with the nutritive effect of the substance, and thus permits multiplication of minute inocula. In general, albumin antagonizes the inhibitory effect of various toxic substances added to bacteriological media (fatty acids, heavy metals, antiseptics) and is known to form complexes with many compounds. Its chief rôle in the present case is probably the binding of traces of free fatty acid released from the Tween.

It is important to mention at this time that most tissues and sera contain lipases which can hydrolyze Tween 80 and release from it free oleic acid; even purified serum albumin is contaminated with this enzyme. The objectionable lipase effect can be minimized by heating the albumin solution to 56° C. prior to its introduction into the medium, or by adding to the latter substances capable of inhibiting lipolytic activity (fluoride for example).

#### GROWTH OF TUBERCLE BACILLI ON AGAR MEDIA

For reasons which are still unknown, no significant growth is obtained when tubercle bacilli are inoculated on the surface of solid media prepared by adding 1.5 per cent agar to the nutrient solution described above. However, if 0.5 per cent serum albumin is added to the same medium, distinct colonies can be recognized within seven to fifteen days, depending upon the strain used and the size of the inoculum. When cultures of avian strains or of the human strain H37Rv growing diffusely in the liquid medium are streaked in dilution on the surface of the Tween-albumin-agar medium, the number of colonies which become visible within ten days corresponds to a bacterial population of approximately  $10^8$  living cells per ml. of liquid medium. It appears likely, therefore, that every cell or almost every cell, or clump of cells, gives rise to a colony, and that under certain conditions and with certain strains the agar method can be utilized for quantitative cell counts. Although all avian strains so far tested have given satisfactory colony counts on the Tween-albumin-agar plates, it must be emphasized that the results obtained with certain human strains have been less consistent. As already mentioned in the case of the liquid medium, addition of glycerol to the agar medium never improves early growth and often prevents the growth of minute inocula. It is also worth repeating that most organic materials (serum, ascetic fluid, etc.) contain lipases which hydrolyze Tween 80 and release from it free oleic acid which exerts a toxic effect on tubercle bacilli.

#### BIOLOGICAL PROPERTIES OF TUBERCLE BACILLI GROWING IN THE PRESENCE OF TWEEN 80

Avian, bovine and human tubercle bacilli, growing diffusely in liquid media containing the water soluble esters of oleic acid—with or without serum albumin—retain their characteristic morphology and staining characteristics. Acid-fast bacilli are readily demonstrated even in cultures only three days old and we have

failed so far to recognize the presence of the non-acid-fast forms which have been described as representatives of very young growth. Several cultures have now been maintained for more than a year with repeated transfers in liquid media containing Tween 80 without any detectable alteration of their morphological and cultural characteristics. These cultures again give rise to the classical mode of growth when they are returned to the standard bacteriological media (egg yolk media for example).

Cultures growing diffusely retain their viability for long periods of time, in particular when serum albumin is added to the medium. For example, cultures of human or avian strains maintained for two months at 37° C. in liquid media with 0.05 per cent Tween 80 and 0.2 per cent albumin contain  $10^8$  to  $10^9$  living bacilli per ml., as determined by colonial counts on agar media or by the dilution method in liquid media.

The cells growing on the surface of the agar medium also appear typical in morphology and staining characteristics. The colonial morphology, however, deserves special mention. Cultures of laboratory strains of human bacilli of high virulence (H37Rv) and cultures directly isolated from human pathological material give on the surface of agar media (containing 0.05 per cent Tween 80 and 0.5 per cent bovine albumin) colonies characterized by smooth contour and glistening surface. When, on the other hand, the same cultures are grown on the surface of agar media of the same composition, but without Tween, the colonies usually appear much smaller and with an extremely ragged outline. It is not known as yet whether this striking difference in colonial morphology corresponds to a fundamental biological difference between the two types of growth, or whether it is only the expression of a physical effect of the environment upon the appearance of the colony.

In addition to the difference in colonial morphology which results from the absence or presence of Tween 80 in the agar medium, other differences have been observed which are almost certainly the manifestation of hereditary variation in the culture (bacterial dissociation). Thus, inoculation of the strain Sigerson<sup>6</sup> on the surface of Tween-albumin-agar medium gives rise at first to a uniform population of round smooth colonies; upon further incubation, however, there appears on the same medium a secondary growth of variant forms which exhibit a rough surface and lacy outline; these colonies give a mixed population of the rough and smooth forms, with a predominance of the former when they are transferred to new Tween albumin agar. Similar results have been obtained with a number of human strains.

*The virulence and immunological characteristics of tubercle bacilli growing diffusely in the presence of Tween 80:* As already mentioned, the H37Rv strain of human tubercle bacillus gives on Tween-albumin-agar smooth colonies which can be repeatedly transferred on the same medium. Identical results have been

<sup>6</sup> We are much indebted to Dr. W. H. Feldman for sending us a culture of the Sigerson strain. Although this strain was isolated from a fatal case of human tuberculosis, our results confirm Dr. Feldman's statements that many of its growth and pathogenicity characteristics are those of an avian strain.

obtained with several other primary cultures obtained from the sputum or spinal fluid of tuberculous patients. Inoculation of these smooth colonies into Tween-albumin liquid medium gives rise to a homogeneous diffuse growth which has been used for a number of virulence tests in guinea pigs, mice and chick embryos.

Guinea pigs infected with 0.05 to 0.01 mg. of five to seven days old cultures develop generalized and progressive tuberculosis resulting in death within three to six weeks following intraperitoneal inoculation and within one to two months following subcutaneous inoculation. It is possible to establish in mice a regularly fatal infection by intraperitoneal injection of human or bovine tubercle bacilli grown in liquid Tween medium. On the basis of these tests, therefore, it appears that cultures growing diffusely in the presence of water soluble esters of oleic acid retain their pathogenic properties.

Cultures growing diffusely in Tween-albumin liquid medium have also been used to infect developing chick embryos either via the yolk sac (seven day old embryo) or directly on the chorio-allantoic membrane (ten day old embryo) (see figures 1 and 2). In both cases macroscopic lesions can be seen on the membrane of the twenty day old embryo following infection with 4 different bovine and 5 different human strains. Of the 4 avian strains so far tested, only one (Sigerson) has been found to produce lesions following direct infection on the chorio-allantoic membrane; infections via the yolk sac gave negative results in the case of all avian strains. It must be emphasized, however, that no convincing information is available concerning the virulence of our strains for other experimental animals and that we have not attempted to determine the extent of the multiplication of the avian bacilli in the infected embryo.

Some of the quantitative aspects of the infection of chick embryos with human bacilli (H37) appear worth emphasizing. Infection via the yolk sac with the larger amounts of culture (0.02 to 0.04 mg.) causes the death of a large percentage of the embryos. Most embryos survive with an inoculum of 0.01 to 0.02 mg; under these conditions, however, there occurs an enormous multiplication of the bacilli within the yolk sac, quantitative enumeration on agar media revealing  $10^8$  bacteria per ml. of fluid following emulsification of the yolk content with saline and glass beads. The chorio-allantoic membranes of these embryos exhibit countless gross tuberculous lesions with a characteristic hematogenous distribution. From 30 to 80 gross lesions could be seen on the membrane infected with 0.001 to 0.002 mg. bacilli, whereas the membrane remained apparently normal when the infective dose was further reduced to 0.0001 mg. No significant lesions resulted from introduction on the membrane of much larger amounts (0.2 mg.) of bacilli killed by heat; it is clear therefore that the effects observed were not due to the nonspecific chemical effect of the material introduced in the form of bacterial bodies but that they resulted from the multiplication of the bacilli in a susceptible host.

Finally, some preliminary studies have been carried out to establish the immunological characteristics of the cultures growing diffusely in the presence of the water soluble oleic esters. When injected into rabbits, the avian and

human bacilli elicit the production of agglutinins for the homologous cultures grown on the standard egg media. In addition to antibodies common to both

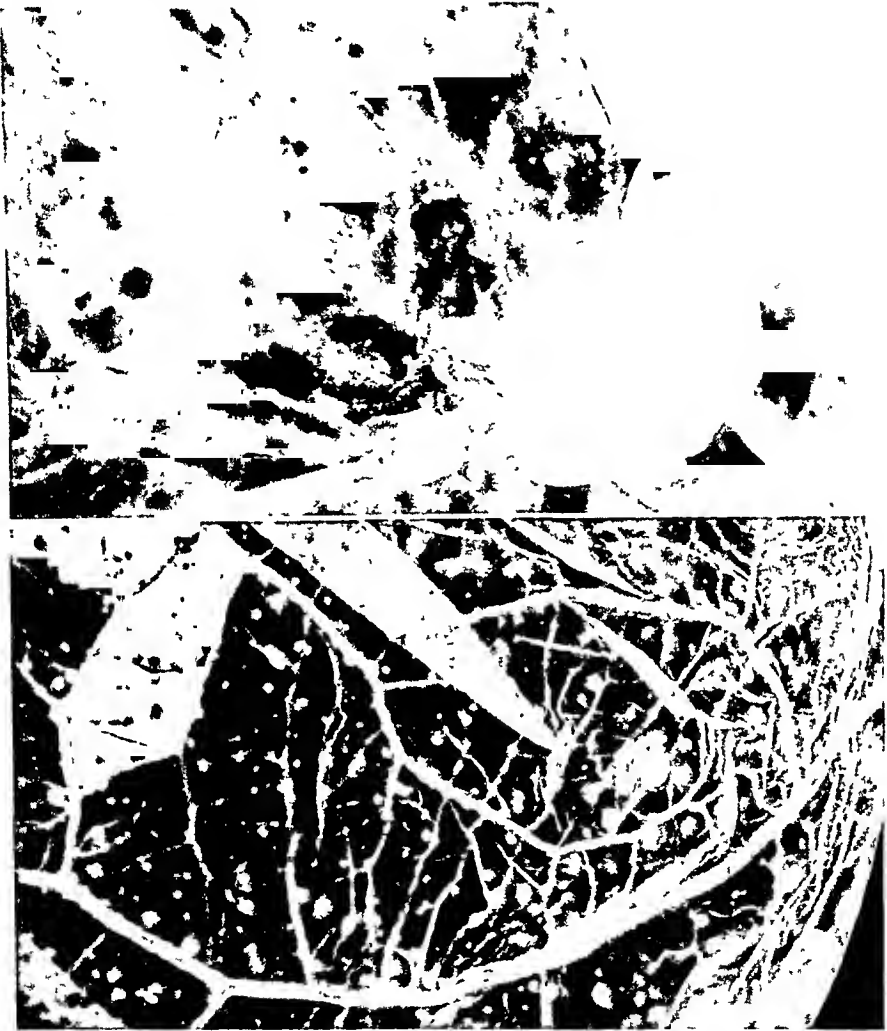


FIG. 1. (Upper) Chorio-allantoic membrane of the developing chick embryo seven days after direct inoculation on the surface of the membrane.

Membrane inoculated on the tenth day of incubation with 0.05 mg. human tubercle bacilli (strain: H37S cultured in liquid medium containing 0.1 per cent Tween 80, 0.1 per cent serum albumin).

FIG. 2. (Lower) Chorio-allantoic membrane of the developing chick embryo ten days after yolk sac inoculation.

Yolk sac inoculated on the seventh day of incubation with 0.015 mg. human tubercle bacilli (strain: Dubos 1 cultured in liquid medium containing 0.1 per cent Tween 80, 0.1 per cent serum albumin).

bacterial types, there are produced agglutinins specific for each type. This can be demonstrated by differential adsorption reactions which will be described in

greater details elsewhere and which permit preparation of sera capable of causing selective agglutination of the avian or human culture<sup>7</sup> (table 1).

Human bacilli growing diffusely in Tween 80 liquid medium (without serum albumin) and resuspended in saline containing 0.02 per cent Tween give homogeneous and stable bacillary suspensions which have been used for agglutination tests with human sera. A few statements will serve to illustrate the results obtained by this method. High agglutination titers were observed with the serum of a patient suffering from retrogressive tuberculosis (titer 1:160 to 1:320) and with the serum of a physician in frequent contact with tuberculous patients (titer 1:80 to 1:160). The sera of several patients with progressive tuberculosis

TABLE 1

*Serological specificity of avian (Kirchberg) and mammalian (H37RV) tubercle bacilli grown in "Tween 80" medium*

SERUM DILUTIONS	NORMAL PRE-IMMUNE RABBIT SERUM		ANTI-AVIAN RABBIT SERUM		ANTI-AVIAN RABBIT SERUM ADSORBED WITH H37RV	
	Kirchberg	H37RV	Kirchberg	H37RV	Kirchberg	H37RV
1:20	—	—	+++	+++	++	—
1:40	—	—	+++	+++	++	—
1:80			+++	+++	+	—
1:160			+++	+++	+	—
1:320			+++	++	+	—
1:640			++	+	—	—
1:1280			+	—	—	—
1:2560			—	—	—	—
1:5120			—	—	—	—
Saline control	—	—				

(Agglutination mixtures incubated at 50°C. for three hours, then overnight at 38°C.)

and of persons without clinical tuberculosis, but with positive tuberculin reactions, gave lower agglutinin titers, varying from 1:20 to 1:80. No agglutinating antibodies could be detected in the serum of 2 tuberculin-negative children or of one patient suffering from milary tuberculosis. Identical results were obtained using as test organisms for the agglutination reaction the standard laboratory strain H37S and the strain isolated from the case of milary tuberculosis mentioned above.<sup>8</sup>

<sup>7</sup> It is important to mention at this time that tubercle bacilli (human and avian) grown in the presence of Tween 80 and injected into rabbits, also elicit the production of antibodies directed against this water soluble ester of oleic acid. In other words, the sera prepared under these conditions contain at the same time antibodies for the bacterial constituents of the injected antigen and other antibodies for the Tween 80 adsorbed on the bacterial surface. These facts are of importance not only because they may be the source of some confusion in the analysis of the immunological behavior of tubercle bacilli grown in the presence of Tween, but also because they establish that the synthetic oleic acid ester can act as a powerful antigen when injected into rabbits in association with tubercle bacilli (table 2).

<sup>8</sup> We wish to acknowledge with thanks the coöperation of Dr. W. McDermott and Dr. R. Gorman of the Department of Medicine of Cornell Medical College and of Dr. H. Bray and Dr. D. Yegian of the Ray Brook Sanatorium who made available to us some of the sera and cultures used in these studies.

These results are not presented to suggest that agglutination reactions can be used as a diagnostic or prognostic test in tuberculosis but only to illustrate the fact that bacilli growing diffusely in the presence of water soluble esters of oleic acid retain specific agglutinability in the presence of the antibodies which may be present as a result of tuberculous infection.

TABLE 2

*Effect of "Tween 80" on agglutination of H37RV in antiserum prepared by immunization of a rabbit with H37RV grown in "Tween 80" medium*

SERUM DILUTIONS	NORMAL PRE-IMMUNE SERUM		ANTI-H37RV RABBIT SERUM (CONTAINING PRECIPITINS FOR "TWEEN 80")	
	Antigen A	Antigen B	Antigen A	Antigen B
1:20	+	—	+++	++++
1:40	+	—	+++	++++
1:80			++	++++
1:160			++	++++
1:320			+	++++
1:640			+	++++
1:1280			+	++++
1:2560			+	+++
1:5120			+	+++
1:10240			+	++
1:20480			+	+
1:40960			+	+
Saline control	+	—		

Antigen A: H37RV, grown on glycerine-egg medium, suspended in saline.

Antigen B: H37RV, grown on glycerine-egg medium, suspended in saline containing 0.02 per cent "Tween 80".

Both antigens were heated at 100°C. for twelve minutes before testing.

(Agglutination mixtures incubated at 50°C. for three hours, then overnight at 38°C.)

#### COMMENTS AND CONCLUSIONS

The media described in the present report were devised to meet the nutritional requirements of certain standard laboratory strains of tubercle bacilli. Although other strains will probably be found to exhibit different or more complex requirements it is encouraging to note that both in other institutions and in our own laboratory it has been possible to isolate tubercle bacilli from a variety of pathological material obtained from tuberculous patients by direct inoculation in the Tween-albumin medium. Of special interest is the fact that positive cultures have been obtained with inocula (sputum, blood, spinal fluid and urine) in which it was not possible to find acid-fast organisms by microscopic examination of concentrated material. It appears possible, therefore, that the results presented here may serve as the basis for the development of more satisfactory techniques for the bacteriological diagnosis of tuberculosis.

Virulent bacilli growing diffusely in liquid media containing the water soluble oleic acid esters retain their characteristic morphology, staining properties, virulence and immunological specificity. The fact that these media permit the

production of young and homogeneous cultures suggests that they may facilitate the study of some of the problems concerned with the epidemiology, pathogenesis, immunity and chemotherapy of tuberculosis.

#### COMENTARIOS Y CONCLUSIONES

Los medios descritos en este estudio fueron elaborados para atender a los requisitos nutritivos de ciertas cepas fijas de bacilos tuberculosos de laboratorio. Aunque probablemente se encontrarán otras cepas que manifiesten requisitos distintos o más complejos, resulta alentador observar que tanto en otras instituciones como en el laboratorio de los A. A. fué posible aislar bacilos tuberculosos de variado material patológico obtenido de tuberculosos, mediante la inoculación directa en el medio de albúmina-Tween. Es en particular interesante el hecho de que se obtuvieran cultivos positivos con inóculos (esputo, sangre, líquido cefalorraquídeo y orina) en que no fué posible descubrir microbios acidorresistentes por el examen microscópico del material concentrado. Parece, pues, posible que el resultado aquí expuesto sirva de base para la elaboración de técnicas más satisfactorias para el diagnóstico bacteriológico de la tuberculosis.

Los bacilos virulentos que proliferan difusamente en medios líquidos que contienen los ésteres hidrosolubles del ácido oleico retienen sus características morfológica, propiedades de coloración, virulencia y especificidad inmunológica. El hecho de que dichos medios permitan la producción de cultivos jóvenes y homogéneos indica que pueden facilitar el estudio de algunos de los problemas enlazados con la epidemiología, patogenia, inmunidad y quimioterapia de la tuberculosis.

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## ADEQUATE DIET IN TUBERCULOSIS<sup>1,2</sup>

FRANCIS M. POTTENGER, JR. AND FRANCIS M. POTTENGER

In a nation made sharply conscious of malnutrition by the figures of the draft for World War II, we are receptive to useful ideas for the improvement of the health of the public. For many years physicians treating tuberculous patients have been working to combat malnutrition, without the reminder of the statistics of draft rejections. During the war, ration boards were empowered to grant extra meat allotments to patients suffering from tuberculosis. It is universally accepted that adequate diet is necessary for the treatment of this disease.

We propose to describe our own experience in the use of diet as a therapeutic agent for treating the tuberculous. Dr. F. M. Pottenger founded the Pottenger Sanatorium for Diseases of the Chest in 1903. Cherishing a firm personal belief that good food formed a sound basis for the treatment of all diseases, he gave primary consideration to the cuisine. His chefs prepared meals as interesting and delectable as those served in a fine hotel. Not only did the patients show an improved state of nutrition, but they anticipated the meals with enjoyment and appeared to adapt themselves contentedly to hospitalization.

With an established policy of good food served attractively, we were ready to make use of the newer knowledge of nutrition as science began to investigate the effects of food on health. Twelve years ago, a special diet was developed for the patients in our institution. The diet was made elective, and about half of our patients chose to receive it. Those who selected their foods without reference to our suggestions, however, were influenced in their choice of foods by the patients on the special diet.

Because of food rationing we have been using a modification of our original diet through World War II. We shall first describe our present menus, and then indicate the changes we shall make when the food market is again normal.

We attempt to provide the vitamin requirements from foods naturally rich in these elements. We alter our food constituents as little as possible by applying low temperatures in cooking. We make extensive use of the hydrophilic colloidal properties of gelatin. We supply an adequate amount of minerals by using relatively crude foodstuffs.

Our breakfast menu is as follows: A cooked whole grain cereal such as rye, oats, barley, wheat or corn, to which is added one-half ounce of raw wheat middlings; one pat of butter; three ounces of 20 per cent raw cream; eight ounces of raw milk; a citrus fruit equivalent to one-half grapefruit or one orange; four prunes; a choice of two eggs and four slices of bacon or a serving of sausage; one slice of whole grain toast; a cup of coffee substitute, and a glass of gelatin drink, containing one-half ounce of gelatin with a suitable flavoring.

Luncheon consists of a meat-stock soup; a meat (when possible, heart, brain, liver, tripe, sweetbreads or kidney); raw liver three times a week; a raw green

<sup>1</sup> From the Pottenger Sanatorium, Monrovia, California.

<sup>2</sup> Read before the Institute of Medicine, Chicago, Illinois, November, 1945.



salad; two cooked vegetables; a dessert such as custard, ice cream, junket or jello, or fruit in season; one slice of whole grain bread with one pat of butter; one glass of gelatin drink; eight ounces of raw milk; one drachm of rice molasses concentrate or one-half ounce of malt extract.

The evening meal follows the luncheon plan except that a roast is usually served in place of other meats. With this amount of food, there is no demand for between-meal feedings.

Whole grains are used in cereals and breads in order to provide adequate minerals. The bread used for all meals except breakfast is made of sprouted wheat and rye and is very rich in the vitamin B complex, inasmuch as it is baked at a temperature of 160°F. The raw wheat middlings are also an excellent source of the vitamin B complex and of vitamin E. The prunes are given for their laxative action.

We serve fertile eggs of hatching quality because of their superiority in estrogenic substances (1). We use certified raw milk because of the presence in this product of important enzymes necessary in calcium metabolism. Experimentally, we have demonstrated that cooked meat and heat-treated milks, when fed to cats, interfere with proper calcification of the bones, enhance susceptibility to bacterial infection and bring about demineralization (2, 3).

Raw liver served in tomato juice is an excellent source of the known necessary minerals and vitamins. We serve other visceral meats whenever possible to provide the patient with an adequate amount of nuclear proteins.

The purpose of the gelatin is to give a hydrophilic colloidal base to the stomach content, reducing the irritation of the gastric mucosa. This is of inestimable value to patients suffering from extensive tuberculous enteritis, most of whom are able to tolerate the diet well, and are apparently aided in the healing of their intestinal lesions.

We find that patients can handle animal fats, particularly the normal fat on meat and butter fats, better than vegetable fats. In salad dressings, we prefer to use olive oil rather than other vegetable oils.

Most patients gain weight on this diet for about three months. However, their tissue tone tends to improve so that they may actually shrink in physical measurements while showing an increased weight. Patients whose disease is extensive and who are almost entirely inactive may develop a good degree of muscle tone in spite of the lack of exercise. The muscular fatigue suffered by tuberculous patients who return to physical activity after long periods in bed is partially avoided by those who have eaten the special diet.

Many patients on this diet correct their bowel habits, even when they have suffered from long standing constipation. In spite of the roughage present, many patients who suffer from tuberculosis of the bowel soon regulate their evacuations and eliminate nocturnal diarrhea. We believe that the special diet improves the nutrition, increasing their resistance to their disease, and cutting down the frequency and severity of gastrointestinal complications.

We have used this diet in the treatment of patients suffering from asthma and allergies, with good results. We have had the experience of seeing positive

tuberculin reactions in many children become negative after a period of time on this diet (4). We feel that the improved dietary has contributed in large measure to this loss of tuberculin sensitivity.

Analysis of our diet, in daily amounts, is as follows (5):

Protein.....	231 g.
*Fat.....	187 g.
*Carbohydrates.....	310 g.
Calories.....	3,840
Calcium.....	1,697 mg.
Phosphorus.....	3,007 mg.
Iron.....	29 mg.
Iodine.....	107 mmg.
Vitamin A.....	19,337 I.U.
Thiamin.....	4,168 mmg.
Riboflavin.....	5,086 mmg.
Nicotinic acid.....	48 mg.
Ascorbic acid.....	120 mg.
Vitamin D.....	107 I.U.

A group of dentists in California, who are alert to the part that nutrition plays in dental health, recently convened for a Seminar<sup>4</sup> at Palm Springs, California. It is of interest to note that their food recommendations closely resemble those which we use at the Sanatorium. This group has worked out a dietary which they advise for maintaining a healthy condition of the teeth and gums. It consists of the following elements, in the daily amounts listed (6):

Protein.....	211 g.
Fat.....	115 g.
Carbohydrates.....	201 g.
Calories.....	2,600
Calcium.....	2,342 mg.
Phosphorus.....	3,060 mg.
Iron.....	27 mg.
Iodine.....	225 mmg.
Vitamin A.....	18,480 I.U.
Thiamin.....	1,560 mmg.
Riboflavin.....	4,335 mmg.
Nicotinic acid.....	53 mg.
Ascorbic acid.....	177 mg.
Vitamin D.....	168 I.U.

Three items which were part of our original diet have been curtailed by World War II. It is our intention to resume their use as soon as materials are

<sup>3</sup> These figures were compiled on a specially equipped I.B.M. Machine by Michael Walsh, M.Sc., San Diego, California. The figures are based on the usual portions and ingredients; allowance must be made for the fact that we do not trim the fat from our meat servings, and our custards and other dishes containing carbohydrates are made with a minimum amount of sugar and additional eggs and milk.

<sup>4</sup> The Second Annual Seminar of Dental Medicine, sponsored by the Southern California State Dental Association and the Oregon State Dental Association at the Desert Inn, Palm Springs, California, October 7 to 12, 1945.

again available. First, we used raw bone meal with our breakfast cereal. We have found that the femur of the steer, ground at low temperatures, provides an excellent source of calcium. It is easily chewed into a gelatinous mass and is more readily assimilable than heat-treated bone meal and other forms of calcium. Second, we used the sprouted Chinese mung-bean in our green salad once a day. These sprouts are rich in vitamins B<sub>1</sub> and C, and contain a small amount of vitamin A as well as diastase, prochlorophyll, minerals and hydrolyzed vegetable protein. Third, we used visceral meats as one-third of the daily meat ration, instead of their occasional use as at this time.

We believe that it is possible to use this dietary in public institutions where the food costs must be closely budgeted. By substituting the less expensive cuts of meats, including visceral meats, by using sprouted seeds of some type as part of a green salad, by using whole grain cereal ground in the hospital kitchen as well as whole grain bread-stuffs, and by cutting down refined carbohydrates, it is possible to adapt this high protein, high fat, low carbohydrate diet for use in public institutions.

*It is our conclusion that the logical basis on which to estimate the cost of food for tuberculous patients is the cost per patient per period of arrestment rather than the cost per patient per day.* If a highly vital diet of slightly greater cost will restore a patient to health in a shorter time than a cheap diet of poor nourishing quality, the end-result is a saving of time and a saving of the tax-payer's money.

We serve our employees a high protein diet without the adjuncts of rice molasses concentrate, malt extract or gelatin. The fact that we have had no known tuberculous infections attributable to employment among our employees in forty-two years is suggestive of the protective value of the food eaten.

One of the foremost names in nutritional research is Sir Robert McCarrison. Following World War I, he performed experiments on rats, monkeys and pigeons by feeding them the diets of the various peoples of India. Ill health was imposed upon these animals comparable to that suffered by the people consuming the inadequate diet (7). We have performed similar experiments on cats in our own laboratory with like results (8).

One of the outstanding experiments with human beings is the Papworth Settlement in England (9). Here tuberculous patients carry on supervised work. Two rules are rigidly enforced: first, that all patients must expectorate into sputum pocket flasks, thus eliminating the possibility of mass doses of infection; second, that all patients must consume an adequate diet. Sir Pendrill Varrier-Jones, in a report in 1936, reported that none of the children born of parents in this settlement showed active infection. He concludes that "the child's resistance to disease is maintained by (a) adequate nutrition and (b) the absence of mass doses of infection."

Wrench (9) sums up the influence of circumstances which predispose human beings to infection as follows: "Living in dark, close alleys and tenements means also faulty food. The impure air of slums means one food, namely, oxygen, being defective, but it means also that people who breathe it have not the money for foods that cannot, like oxygen, be got for nothing. Alcohol in

excess destroys the appetite. So do the poisons of such diseases as diabetes and kidney disease. So does confinement in prisons, workhouses, and workshops. None of the people debilitated by such places or such diseases eats heartily of good food. As to catarrh of the respiratory passages, that in itself was produced by McCarrison and also by Mellanby by faulty food. The barrier breaks down before the catarrhal microbes. A mass attack of tubercle bacilli may do the rest."

#### SUMMARY

It is a universally accepted fact that adequate diet is necessary for the treatment of tuberculosis. Our experience at the Pottenger Sanatorium has borne out the value of the high protein, high fat, low carbohydrate diet, rich in natural vitamins, in the treatment of active tuberculosis.

Twelve years ago we adopted an elective diet which we have made available to all our patients wishing to elect it since that time. There have been as few substitutions as possible throughout the war years. We provide a daily intake of approximately 225 g. of protein, 250 g. of fat and 235 g. of carbohydrate. We attempt to supply the vitamin and mineral requirements from foods naturally rich in these elements. We alter our food constituents as little as possible by applying low temperatures in cooking, and we make extensive use of the hydrophilic colloidal properties of gelatin.

We have found that this vital diet apparently increases the resistance of the tuberculous individual to his disease, and improves muscle tone, often in spite of lack of exercise. We have subsequently used this same type of diet in the treatment of a group of allergic children, with good results.

It is our conclusion that the logical basis on which to estimate the cost of food for tuberculous patients is the *cost per patient per period of arrestment*, rather than the cost per patient per day. If a highly vital diet of slightly greater cost will restore a patient to health in a shorter time than a cheap diet of poor nourishing quality, the end-result will be a saving of time and a saving of the tax-payer's money.

We believe that a highly vital diet can build the resistance of an individual to his disease, and help him to maintain his health so as to continue as a useful member of society.

#### SUMARIO

Es un hecho aceptado universalmente que para el tratamiento de la tuberculosis se necesita una alimentación adecuada. Nuestras observaciones en el Sanatorio Pottenger comprueban el valor de una dieta alta en proteína y grasa, escasa en hidratos de carbono, y rica en las vitaminas naturales, para el tratamiento de la tuberculosis activa.

Hace 12 años adoptamos una dieta que desde entonces hemos puesto a la disposición de los enfermos que deseaban seguirla. Durante los años de la guerra hemos hecho en ella el menor número de cambios posible. La ingestión diaria es aproximadamente de 225 gm. de proteína, 250 gm. de grasa y 235 gm. de

hidratos de carbono, tratándose de llenar los requisitos de vitaminas y sales minerales por medio de alimentos naturalmente ricos en dichos elementos. Los componentes alimenticios son alterados lo menos posible, aplicando temperaturas bajas para la cocción, y utilizando en gran escala las propiedades hidrófilo-coloidales de la gelatina.

Hemos observado que esta dieta vital aumenta aparentemente la resistencia del tuberculoso a la enfermedad, y mejora la tonicidad muscular, a menudo a pesar de la falta de ejercicio. Hemos utilizado después la misma clase de dieta en un grupo de niños alérgicos, con buenos resultados.

Nuestras conclusiones son que la base lógica para calcular el costo del alimento de los tuberculosos es el *costo por enfermo por período de estacionamiento*, más bien que el costo diario por enfermo. Si una dieta muy vital que cuesta un poco más restablece la salud en menos tiempo que una alimentación barata mas poco nutritiva, al final de cuentas economizárá dinero y ahorrará los fondos de los contribuyentes.

A nuestro parecer, una alimentación muy vital reforzará la resistencia del individuo a la enfermedad, y lo ayudará a mantener su salud, continuando así como miembro útil de la sociedad.

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# TUBERCULOSIS AND HUNGER EDEMA

PANAYIOTIS CHORTIS<sup>1</sup>

During the trying period of 1941-1942 when Greece suffered privations, hardships and starvation, its hospitals were filled almost exclusively with patients suffering from hunger edema. Opportunity was presented to observe and follow great numbers of newly admitted patients in the Hospital-Sanatorium of Sotiria who showed extensive hunger edema and progressive pulmonary tuberculosis. Most of these patients died shortly after admission; others, with the benefit of complete bed-rest and the meagre hospital diet, showed temporary improvement in their general health and disappearance of the edema, but eventually succumbed to an acute progressive form of tuberculosis, since no type of collapse therapy was applicable. In a few patients showing slight and localized pulmonary changes with a slight degree of hunger edema, it was possible to induce pneumothorax as soon as complete disappearance of the edema was evident. It is probable, then, that in the course of hunger edema in tuberculosis patients acute exudative forms become evident with eventual fatal result.

To date no work has been published on the question of tuberculosis and hunger edema, though a great number of authors have written about hunger edema in nontuberculous conditions. In order to study the problem fully, complete clinical, biochemical and histopathological studies were attempted, but it took over two years to accomplish them because of the difficulties of research during the enemy occupation.

A total of 108 patients were studied. These were divided into three groups according to the severity of their general condition, extent of edema and development of the pulmonary changes. Of the 75 cases in group 1 with severe edema and diffuse bilateral pulmonary tuberculosis there were no survivals. In group 2, composed of 23 patients with diffuse edema and extensive changes in one lung, 2 have improved, one has remained stationary and the rest have died; in group 3 with 10 cases presenting slight edema and localized pulmonary involvement, 6 were apparently cured, 4 have shown considerable improvement and no deaths have occurred.

It was evident from the patients' histories in all three groups that most of them suffered lack of adequate nourishment over long periods of time, especially a total lack of animal proteins, and were getting only a small amount of vegetable protein and fat. As a result of this diet a considerable loss of body weight was noted with easy fatigue, mental and bodily sluggishness and finally the appearance of localized or diffuse edema. The extent of edema has been related to the severity of the pulmonary involvement, and it was found that diffuse edema appeared mostly in patients with severe pulmonary disease. The edema appeared first in the ankles, eyelids, then in the lower limbs and face and finally spread all over the body. The appearance of this edema was

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similar to that seen in nephrosis. After the disappearance of edema the skin lost its elasticity and resembled a folded bag containing the skeleton. Hunger edema, as we noticed, vanished rapidly in those patients who received supplementary animal proteins in addition to the regular sanatorium food.

The main points by which the progressive tuberculosis in these patients with hunger edema was evident were frequent and prolonged hemoptysis and gradual increase in fever. Contrary to the opinion of Gerhartz and Moritz, who report that they observed bronchitis, bronchopneumonia and lobar pneumonia in the course of hunger edema without fever and with bradycardia, we have generally noted a feverish course with severe prognosis in the acute pulmonary infections as well as in pulmonary tuberculosis. In these patients the temperature rose from 99.3° to 103°F., especially in the evening hours, and only in the last stages of the disease did the temperature fall below normal. Fever was especially high in exudative tuberculosis and lasted until resistance of the organs ceased. Cough was troublesome and expectoration abundant, the quantity of sputum being related to the extent of the edema. Hemoptysis was the most common symptom in cases of long duration and did not respond to the usual hemostatic drugs. On auscultation fine moist râles were found on inspiration with localized puffing breathing which in a few days was transformed into cavernous breathing. These findings grew in number and intensity in proportion to the extent of the edema and changed day by day because of the rapid development of the pulmonary changes. In patients in whom the tuberculous changes were recent and artificial pneumothorax was applied as soon as the edema had disappeared, the course of the disease was very favorable. In the circulatory system the most common symptom found was tachycardia, in contrast to most authors who have reported bradycardia which is considered pathognomonic of hunger edema in nontuberculous patients. We attribute this tachycardia to the coexistent tuberculous toxemia and to the myocarditis occurring in the rapid development of tuberculosis. In respect to the various other systems we have observed diarrhea alternating with a dysenteric syndrome and a considerable decrease of gastric acidity, polyuria, as well as mental disturbances, consisting of intellectual clouding, delirium and amnesia, symptoms which were improved following spinal puncture.

Blood studies showed a great disturbance in the equilibrium of the colloidal system, consisting of a considerable decrease in the protein of the blood serum which in certain cases dropped to 1.4 per cent. A diminution of the total protein was noted, while the globulin remained at a normal level. Red blood cells were reduced to about 2 to 3 millions. Blood platelets were also reduced to 80 to 100,000, while the hemoglobin was 55 to 75 per cent, so that a hypochromic anemia was evident. Chlorides in the blood serum were almost always increased, in contradistinction to the blood sugar which was found far below normal levels.

#### PATHOLOGICO-ANATOMICAL FINDINGS

The most common findings were excessive dryness of the skin, loss of subcutaneous fat tissue and great atrophy of the musculature. A great collection

of fluid in the pleural cavities was noticed in 96 per cent of cases. The lungs were generally hyperemic with diffuse exudative lesions and extensive perifocal lymphocytic infiltrations (figure 1). The air cells were generally full of exudate and the bronchial mucosa was edematous. In over half of the cases, the pericardium was filled with fluid and the heart muscle was anemic and distended, containing a minimal amount of blood. In 75 per cent of cases we found free fluid in the peritoneal cavity. The intestines were distended and showed diffuse hyperemic lesions of the serous membrane. In about 58 per cent of cases, we found ulcerated nodules in the intestinal mucosa with swelling of the serial interintestinal ganglia. These ulcerations showed every evidence of their tuberculous nature and often were localized in the ileocecal valve and in the small intestine and very rarely in the mucosa of the large intestine. The liver and spleen, as well as other viscera and endocrine glands, showed a decrease in weight and complete disappearance of fat tissue. The brain commonly was hyperemic and the cerebral cavities full of cerebrospinal fluid. In 4 per cent of the cases we noticed large tubercles localized in the cerebellum and the pons.

In order to make a comparative study we made a pathologico-anatomical investigation of 20 patients who had died of progressive pulmonary tuberculosis or some complication without hunger edema, inasmuch as they had been fed, up to the last moment, with large quantities of proteins. In these cases the subcutaneous fat tissue, though reduced, was present. The atrophy of the muscles was insignificant. The elasticity of the skin was preserved and the pulmonary changes, although extensive, presented no important circumfoal and widespread swelling and the bronchial mucosa was not edematous. The weight of the viscera and the endocrine glands was normal, while some of them, especially the liver, was overweight due to passive congestion.

#### HISTOLOGICAL FINDINGS

We also made detailed histological examinations of all the viscera and glands of internal secretion. To make a comparative study, we investigated 24 patients who had died of tuberculosis and hunger edema and 6 patients who had died of progressive tuberculosis or some other complication without hunger edema.

In these investigations we noted the following: The lungs showed cloudy swelling of the alveoli and an extensive edema of the connective tissue between them, a filling of the alveoli with exudate, and edema of the bronchial mucosa (figure 2). In the brain we found hyperemia of the capillary vessels, edema of the cerebral tissue, turbid swelling of the endothelial cells and spotty hemorrhages around the capillary vessels. The nuclei of the nerve cells presented changes in size and appearance. The neuroglia had lost its compact appearance and presented a fibrous web; in the small interstices were transparent pores which were filled with liquid (cerebral swelling). In the liver we found extensive cloudy swelling of the protoplasm of the hepatic cells with serous impregnation of the interstitial tissue in which many tubercles were localized (figure 3). In the kidneys we found cloudy swelling of the protoplasm of the epithelial cells of the uriniferous tubes with overdistention of Bowman's capsules by exudate, resulting in a deformation of the tubule, (figure 4). We also observed infrequent tubercles





in the conjunctival interstitial tissue. In the heart, besides the cloudy swelling of the sarcoplasm of the muscle cells and the serous impregnation of the interstitial tissue, we found also a separation of the muscle fibers at their point of junction (figure 5). An abundance of small localized tubercles were also noticed in the connective tissue. In the spleen we observed a thickening of its capsule and its interstices with a decrease in number and size of the splenic follicles, with small anemic ones imprisoned in the parenchyma due to the obstruction of the capillary vessels by the continuous presence of bacilli in the circulating blood. We also found infrequent tubercles in the interstitial connective tissue. In the suprarenal gland we found a marked decrease in fat substance in the cortex, a degenerative atrophy of the medulla and an occasional tubercle in the interstitial tissue (figure 6). In the pituitary gland we noted that the epithelial cells had not maintained their natural texture but presented cellular division with atrophy. A slight hyperplasia of the interstitial tissue with lymphocellular infiltration was noticed (figure 7). In the thyroid gland disappearance of the colloid substance of the glandular vesicles was noticed with a serous impregnation of the interstitial connective tissue and a liquid infiltration between the walls of the glandular vesicles, which sometimes presented a hyperplasia of their glandular cells (figure 8). In some cases we found tubercles in the interstitial connective tissue. In the pancreas we found cloudy swelling of the protoplasm of the endothelium of the glandular cells with serous impregnation of the interstitial connective tissue. Occasionally, we also noticed hyperplasia of the cells of the islands of Langerhans.

Thus, besides cloudy swelling of the protoplasm of the cells of the various viscera and endocrine glands and serous impregnation of their interstitial tissue, that is, edema, we also noticed many tubercles in the parenchyma of viscera and endocrine glands and chiefly in organs in which tubercles are seldom seen, as for example the thyroid gland, pancreas and pituitary gland. We have at-

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FIG. 1. (Upper left.) Lung, showing intense perifocal lymphocytic reaction around a necrotic tuberculous lesion (low power).

FIG. 2. (Upper right.) Lung, showing extensive edema of the connective tissue and cloudy swelling of the alveolar cells (high power).

FIG. 3. (Top centre left.) Section of liver showing cloudy swelling of the liver cells, edema of the interstitial tissue, lymphocytic infiltration and a large tubercle.

FIG. 4. (Top centre right.) Section of kidney, showing cloudy swelling of the epithelial cells of the uriniferous tubes, a collection of serous exudate in Bowman's capsule and deformation of the tubule.

FIG. 5. (Bottom centre left.) Heart muscle, showing separation and breaking of the muscle fibres at their point of junction, cloudy swelling of the sarcoplasm and edema of the interstitial tissue.

FIG. 6. (Bottom centre right.) Suprarenal gland, showing decrease in fatty substance of the cortex, edema of the interstitial connective tissue and atrophy of the medulla.

FIG. 7. (Lower left.) Pituitary gland, showing hyperplasia of the interstitial tissue with a slight degree of lymphocellular infiltration.

FIG. 8. (Lower right.) Thyroid gland, showing decrease of colloid substance of the glandular acini and varying size of the acini and edema of the interstitial tissue.

tributed this to the frequently occurring bacillema, as well as to the considerable decrease of the general and localized resistance of the organism in patients with tuberculosis and hunger edema.

In the histological study of the parenchyma of the viscera and endocrine glands in the patients who had died of tuberculosis without hunger edema, since up to their last moment they had been fed with animal protein and fats, we did not notice any changes in the parenchyma of any organs except the lungs and very rarely fatty degeneration of the liver. The fat tissue of the viscera, though decreased, was present and nowhere did we see cloudy swelling of the cellular protoplasm or serous impregnation of the interstitial tissue.

From the above findings it appears that, during the course of hunger edema in tuberculous patients, the edema is not limited to the skin and subcutaneous connective tissue but extends also to the parenchyma of all the viscera and endocrine glands.

#### DISCUSSION

The above are, in brief, the chemical, biochemical and histopathological findings which we have observed in our cases. Let us now see how the rapid evolution of tuberculosis in patients with hunger edema can be explained. Among the known causes which produce a considerable decrease in the resistance of the organism against tuberculosis, the principal place is occupied by undernourishment, a fact which was demonstrated during the first World War when the morbidity and mortality from tuberculosis showed considerable increase. Therefore, during the course of hunger edema the immunological resistance of the organism is considerably decreased and at the same time the local tissue resistance is also diminished. This is due to cloudy swelling and serous impregnation of the parenchyma of the viscera, chiefly in the lung tissue, where the Koch bacilli, finding a favorable soil for development and lack of resistance because of the edema, disseminate through the pulmonary parenchyma. Thus tuberculous foci are created with circumfocal infiltrations. At the same time the bacilli, penetrating into the blood-stream, form new foci in the walls of the viscera because of the decreased local tissue resistance. This is why tuberculosis in the course of hunger edema assumes an exudative aspect with rapid evolution. The cause of the great decrease in organism resistance is not only the lack of food intake, especially those foods containing protein, but also the coexisting protein poisoning which occurs in the organism due to the incomplete metabolism of the organism's proteins. As a result of these two causes there is a disturbance of the equilibrium of the colloidal system and a marked decrease in the most vital protein of the blood serum, the albumen, the quantity of which plays an important rôle in all biological properties of the organism. However, with the exception of these biological factors which cause the marked decrease in immunological resistance of the organism, there are other mechanical factors contributing to the rapid development of tuberculosis, as for instance, the serous impregnation of the lung tissue, the cloudy swelling of the alveoli, the extensive circumfocal swellings, the edema of the bronchial mucosa and the ob-

struction of their lumina. All these factors contribute to a great decrease in the respiratory surface and such a diminution results in the increase in frequency and intensity of the respiratory movements, producing an aggravation of the pulmonary lesions, which contributes to the rupture of the altered alveoli and the rapid development of the disease. As to the explanation of hunger edema we completely agree with the opinion of those authors who believe that the lack of animal proteins and their vitamins is its principal cause.

We do not believe that the lack of fat, as Zondek claims, constitutes the basis for the appearance of the edema because, as is known, fat as well as carbohydrates can be replaced by an equal quantity of protein or carbohydrate, while on the contrary animal protein cannot be replaced with carbohydrate or fat. Moreover, considering the fact that hunger edema is influenced very much by the administration of animal protein, and that no organic histological changes were found, we contend that the formation of hunger edema is due to biochemical disturbances in the blood constituents and particularly to a great decrease of albumen.

Obviously, the biological properties of the blood plasma depend on the surface tension of the colloidal molecules which links them with each other, and to the electric charge which tends to keep them apart. The greater the surface tension and the electrical charge the smaller are the different protein molecules. The electric charge also acts in opposition to the surface tension because, while the surface tension keeps the colloidal molecules attached to each other, the electric charge keeps them apart. The equilibrium of the colloidal system is based on the counterbalancing of these two tensions. But with the decrease of albumen whose molecules are small and hydrophilic and consequently have a higher osmotic pressure than the molecules of globulin which are coarse and difficult to dissolve in water, there comes a rupture of the equilibrium of the colloidal system, resulting in decrease of the osmotic pressure of the plasma. The decrease in osmotic pressure which normally averages from 38 to 40 cc. to 10 to 20 cc. of water in severe cases is followed by disturbance in the intravascular equilibrium. The watery substances of the blood, not being retained in the vessels due to the great decrease of osmotic pressure, but at the same time being kept back by the predominating intravascular pressure, come out of the vessels into the tissues and provoke edema.

This opinion is supported by the fact that immediately after the allowance of a sufficient quantity of animal protein, when an increase in albumen in the blood serum is noticed and consequently an increase of the osmotic pressure, absorption of the watery ingredients from the tissues into the vessels and disappearance of edema occur.

#### SUMMARY

On the basis of systematic, clinical, biochemical and histological study of 108 patients suffering from tuberculosis with hunger edema, it is concluded that the common histological changes in all the viscera and endocrine glands during the course of the disease consist of cloudy swelling of the protoplasm of the parenchymal cells, serous impregnation of their interstitial tissue and complete disappearance of the fat vesicles. Tuberculous lesions in the viscera were very

frequent, even in those glands in which tuberculosis is usually very rare, as for instance in the thyroid gland, pancreas and pituitary gland. This frequent localization was due to a frequently noticed bacilemia and to the decrease of local resistance of the different organs owing to the edema of the parenchyma.

It is further suggested that the hunger syndrome appears principally in tuberculous patients in whom previously existing or recently developing pulmonary tuberculosis assumes an exudative form with rapid progression. It is also believed that the rapid progression of pulmonary lesions is due to: (1) biological factors contributing to the great decrease in the general immunological resistance against tuberculosis; and (2) mechanical factors contributing to the increase of the respiratory function of the lung, that is, to the enlargement of the respiratory damage which causes rupture of the altered lung fibres and extension of the disease.

As regards the pathogenesis of hunger edema in tuberculous patients, the author suggests that it is due to prolonged lack of animal protein, with the result that the organism consumes partly his own protein, producing protein poisoning, and to a great decrease of the most vital protein of the blood serum, that is, albumen, which has an important function in the biological processes of the organism.

#### SUMARIO

Tomando por base el estudio sistemático, clínico, bioquímico e histológico de 108 enfermos que padecían de tuberculosis acompañada de edema de hambre, dedúcese que las habituales alteraciones histológicas observadas en todas las vísceras y glándulas endocrinas durante la evolución de la enfermedad consisten en degeneración turbia del protoplasma de las células parenquimatosas, impregnación serosa del tejido intersticial de las mismas y desaparición total de las vesículas de grasa. En las vísceras las lesiones tuberculosas resultaron muy frecuentes, aun en las glándulas en las que suele ser rarísima la tuberculosis, por ej., la tiroides, el páncreas y la hipófisis. Esta frecuente localización debióse a una bacilemia bastante común y a la disminuída resistencia local de los diversos órganos a causa del edema del parénquima.

Señálase además que el síndrome de hambre aparece principalmente en los tuberculosos en los que una tuberculosis antigua o reciente reviste forma exudativa con agravación rápida. También parece que la rápida agravación de las lesiones pulmonares procede de: (1) factores biológicos que contribuyen a la gran disminución de la resistencia biológica general a la tuberculosis; (2) factores mecánicos que contribuyen al aumento de la función respiratoria del pulmón, es decir, al incremento de la lesión pulmonar que provoca la rotura de las fibras alteradas y la difusión de la enfermedad.

Con respecto a la patogenia del edema de hambre en los tuberculosos, sugiere el A. que se debe a prolongada carencia de proteína animal, dando esto por resultado que el organismo consume en parte su propia proteína, produciendo intoxicación proteínica, y también a una gran disminución de la proteína más esencial del suero sanguíneo, o sea la albúmina, que desempeña una importante función en los procesos biológicos del organismo.

# TUBERCULOSIS AMONG PERSONS OF JAPANESE ANCESTRY IN THE UNITED STATES

DONNELL W. BOARDMAN<sup>1,2</sup>

With the lifting, on January 2, 1945, of the Exclusion Order affecting all persons of Japanese ancestry in the Western Defense Command (western Washington and Oregon, California and southwestern Arizona) and with the subsequent rescission of all Army exclusion and segregation orders against individuals of this group, more than 100,000 persons formerly affected by the evacuation became free to resettle in any part of the United States. It is estimated that a little more than 50 per cent will eventually return to west coast homes or neighborhoods from which they were evacuated. The remainder will have found new homes throughout the rest of the country. Thus, any health problem peculiar to this group becomes of interest to most of the states of the Union.

Inasmuch as most of this group are either native to or one generation removed from Japan, it is significant that tuberculosis was reported to be the third cause of death in that country in 1934. Discrepancies exist in the reported mortality figures of recent years in Japan from as low as 130 to 140 per 100,000 in 1934 to 206.8 in 1936 and 1938. The latter figures appear to reflect the true situation more accurately (table 1). The incidence of tuberculosis in Tokyo in 1945 has been estimated at approximately 22 per cent.<sup>3</sup>

Existing tuberculosis mortality statistics for persons of Japanese ancestry in this country show a substantially better situation here. In 1940 there were 144 tuberculosis deaths reported among the 127,000 Japanese and Japanese-Americans of the nation, an incidence of only 113.5 per 100,000. However, in that year the national tuberculosis mortality rate was 45.9. Table 1 shows a similar situation obtaining in California, where the Japanese death rate in 1940 was exactly double that for the state population as a whole. Approximately 95,000 of the 127,000 Japanese were settled in California, distributed fairly proportionately throughout the state, in urban and rural areas.

It is important, then, to determine at this time whether the long-assumed high incidence and death rate for tuberculosis among persons of Japanese ancestry is real or apparent.

It is our purpose to show from available data arising from observation of over 8,500 evacuated Japanese for varying periods up to two and one half years: (a) the prevalence of reinfection pulmonary tuberculosis within this group; (b) the percentage of (frankly) active cases and of cases in need of further supervision. A brief discussion of related factors is included.

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<sup>3</sup>Time Magazine, September 17, 1945.

## MATERIAL FOR STUDY

The Colorado River Relocation Project at Poston, Arizona was one of the ten population centres established under the War Relocation Authority for the accommodation of the people evacuated from the West Coast area in 1942. Its population varied from a peak of 17,867 in August, 1942 to 11,000 to 12,000 at the beginning of 1945. Poston relocated its last evacuees on November 23, 1945. Leighton (1), in his recently published book *The Governing of Men*, graphically describes Poston, its background, its material and operational features and, best of all, its psychological pattern, mass and individual.

The following comments on background are pertinent to our discussion. The people of Poston had had pre-war homes and residence for twenty to forty years in all sections of California, notably in Los Angeles, the Imperial Valley of southern California, the coastal area south of San Francisco, the San Joaquin Valley in

TABLE 1  
*Comparative mortality rates from tuberculosis*  
1911-1940  
(Deaths per 100,000 inhabitants)

YEAR.....	1911-1913	1920	1925	1930	1935	1936	1938	1940	PER CENT DECREASE	
									1920-38	1935-40
Japan.....	215	224	194	186	190	206.6	206.8		7.7	
U. S. A.....	135 -152	114	84.8-86.7	71.5	55.1	55.9	49.1	45.9	56.0	16.7
California.....	198.3-203.9	152.6	127.3	98.6	71.4	71.6	60.3	56.0	61.1	21.6
Japanese in California*.....					130	138	111	112		13.8

*Note:* Compiled from statistics published in the Annual Epidemiological Report, 1935, the Public Health Reports of the United States Public Health Service, and the Weekly Bulletins of the California State Department of Health.

\* Computed on the basis of 1940 Census Bureau Population figures.

central California, and in the neighborhood of Placer County in eastern California. The San Francisco Bay area was significantly represented. Except for the Los Angeles contingent, they constituted a farming and small-town community population. The age distribution was typical of the entire group in this country. There were high percentages of adolescents (15 to 20 years) and young adults and of late middle-aged and elderly persons, a smaller group of runabouts (3 to 8 years), and an abnormally small proportion of the 30 to 45 year-olds.

Although the Center was divided into three camps several miles apart, with a population ratio of 9 to 4 to 5 in Camps I, II and III, respectively, basic health operations were conducted as a unit from a 250-bed U. S. Army-type station hospital in Camp I. Although dispensary work was conducted in Out-Patient Clinics in Camps II and III, all hospitalizations, X-ray and laboratory work etc., took place in the hospital.

The population was housed in regulation size Army barracks, divided into six variously sized one-room apartments. The barracks were arranged in groups, fourteen in a block, and four or six blocks to a "quad" or "roku" (from the Japanese meaning six). In the block two rows of seven barracks were separated by a communal laundry, a boiler-room, and a latrine, divided into men's and women's sides. The latrines contained showers (no tubs), and a number of paired hot and cold water faucets spilling into a room-long trough of galvanized iron served as wash-basins. The block mess-hall served all the meals for the block's population (250 to 280). One other building was designed for a recreation hall, but few of these buildings ever became available for recreation. They served instead to house the stores, churches, express offices, welfare offices, nursery schools, or even additional housing.

#### METHOD OF STUDY

The work which provided the basis for this study was conducted in three distinct phases during the period from May, 1942 to February, 1945. During this period 8,652 of the population had at least one roentgenogram of the chest, either a 4" x 5" photofluorogram or a standard 14" x 17" acetate film.

During the *first phase*, in the early days of the Center's operation, May, 1942 to July, 1943, hospital facilities and professional and semi-professional procedures were on an emergency basis. In this period of stress and social unrest, the development and causes of which are the subject of Leighton's (1) book, it was impractical to try to enlist the coöperation of the community in a wide-spread health program. This was possible only after the recognition and resolution, by the end of 1942, of some of the basic problems of community life.

Tuberculosis survey examinations were not conducted. Health educational motion-pictures and discussions were emphasized, however, and valuable ground-work was done in informal education of the people for the mass survey which was to take place. Roentgenograms other than those indicated in the course of clinical work were limited to hospital workers, tuberculosis contacts and some mess-hall workers.

This program was under the direction of Dr. K. Kasuga, an evacuated Japanese-American with training in chest diseases and now for more than two years in the Army of the United States, Medical Corps. Through the establishment of his Chest Clinic and the group discussions and lectures, he caught the interest and confidence of the people, preparing them for the coöperation they showed during the subsequent mass survey. He was also particularly successful in uncovering and putting under treatment a high proportion of young adults with disease susceptible to sanatorium care.

The *second phase*, that of mass survey, took place from July to October, 1943. It would have been impossible, or at least necessarily longer and less thorough, without the introductory aspects of the first phase. In this period approximately 5,100 persons over the age of 15 years were examined by means of a United States Public Health Service 4" x 5" photofluorograph unit, under the direction of Dr. Herman E. Hilleboe, Director of Tuberculosis Division of U.S.P.H.S. Three thousand six hundred of these people were chosen with block residence the only selective factor. An additional 1,400 were mess-hall workers from all three



camps. The survey was unusually complete, the delinquents being sought out personally and almost invariably being persuaded to submit to examination. It was estimated by one member of the survey team that less than 10 persons were missed within the scope of the survey.

Tuberculin testing of 2,650 persons of all ages was done under the direction of the survey group by a public health nurse in October, 1943, as a part of this second phase of the study. Doses of 0.1 and 1.0 mg. of Old Tuberculin were used.

*The third phase* of the program extended from January, 1944 to February, 1945. During this time the results of the previous two periods were consolidated and amplified.

(a) Measures were taken to continue survey filming within existing limitations. Several hundred mess-hall workers, almost 200 school teachers and school employees and 200 or 300 high-school graduates were examined. Also a particular effort was made in this period to follow up family contacts of known cases.

(b) The Chest Clinic was expanded to include the follow-up by appropriate roentgenological, clinical and laboratory examinations of all cases of reinfection type pulmonary tuberculosis. Active or questionably active cases of primary tuberculosis or pleurisy with effusion, uncovered during any of the three periods, were also kept under observation. The objectives of the Clinic were two-fold: (1) clinical confirmation of diagnosis, guidance of the patient and treatment of the disease; and (2) estimation of the dynamic status of the disease process for classification and statistical purposes.

As tuberculosis carries a heavy social stigma among the Japanese, care was taken to include the follow-up in the Chest Clinic of all nontuberculous chronic pulmonary disease and a number of cardiac cases so that a visit would not automatically stigmatize the patient as tuberculous. It is believed that this practice, together with its wide verbal advertisement, was helpful to the desired end.

Patients seen in the Chest Clinic routinely had a complete blood count, urinalysis and erythrocyte sedimentation rate done before the visit. Examinations of sputa were deferred till after the clinic interview, at which time the technique of sputum collection and the desirability of conscientious effort were explained. Since this explanation was time-consuming when an interpreter was necessary, sputa were ordered only when there appeared a likelihood of getting a positive finding. Positive sputa from out-patients were infrequent. Hospitalization was occasionally required of the patient and the contents of the fasting stomach were searched for acid-fast bacilli on three consecutive mornings. Clinics were held in the afternoon. Temperature, pulse rate and weight were recorded. Routine physical examination included inspection of throat and chest and percussion and auscultation of heart and lungs.

Routine tuberculin and coccidioidin skin testing of all patients was an objective, but uniform success was not obtained. However, since there were sporadic cases of pulmonary coccidioidomycosis in Poston, all cases offering the slightest suggestion of a differential diagnostic problem were tested for both diseases.

Although complete blood counts and routine urinalyses were done in all cases seen in the Clinic, these failed to give useful information. It was felt that an elevated sedimentation rate was of more significance than a normal rate. Examinations for acid-fast bacilli were confined to the stained smears of concentrated twenty-four hour sputum specimens or of concentrated fasting gastric contents.

## RESULTS

*First phase:* In his report to the Principal Medical Officer before entering the Army in October, 1943, Dr. K. Kasuga reported the discovery of 149 cases of

TABLE 2

*Chest X-ray survey report, Colorado River Relocation Center, Poston, Arizona*

Survey conducted July to October, 1943, under the direction of United States Public Health Service

Number of people X-rayed..... 5,079

X-RAY FINDINGS	TOTAL		14" x 17"		4" x 5"	
	Number	Per cent	Number	Per cent	Number	Per cent
Reinfection tuberculosis.....	233	4.6	196	3.9	37	0.7
Primary tuberculosis.....	38	0.7	19	0.4	19	0.4
Suspicious tuberculosis.....	6	0.1			6	0.1
Pleurisy.....	91	1.8	26	0.5	65	1.3

## Distribution of reinfection by stage of disease

	TOTAL		DIAGNOSED ON	
	Number	Per cent	14" x 17" Number	4" x 5" Number
Reinfection tuberculosis.....	233	100.0	196	37
Minimal.....	189	81.1	155	34
Moderately advanced.....	42	18.0	39	3
Far advanced.....	2	0.9	2	

reinfection type pulmonary tuberculosis from the opening of Poston in May, 1942 to July, 1943, when the United States Public Health Service survey was started. Of these, 57 cases were hospitalized, indicating an activity rate of at least 38.2 per cent. In this period the Poston X-ray Department examined approximately 2,000 people, of which an estimated 80 per cent had roentgenograms of the chest. Thus the prevalence of reinfection pulmonary tuberculosis among the 1,600 presenting themselves for chest X-ray films in this period was over 9.0 per cent.

*Second phase:* The results of the 4" x 5" photofluorographic survey conducted from July to October, 1943 are shown in table 2. The tabulation is adapted from the analysis compiled by the United States Public Health Service in March, 1944.

TABLE 3

*Results of tuberculin tests with 1:1000 and 1:100 dilutions of Old Tuberculin in 2,645 people of Japanese ancestry in Poston, Arizona, October, 1943, by sex and age*

AGE GROUPS	NUMBER TESTED			NUMBER POSITIVE			PERCENTAGE POSITIVE		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
All ages	2,650	1,308	1,342	1,753	905	848	66.2	69.2	63.2
Under 9	424	207	217	160	77	83	37.7	37.2	38.2
10-19	691	312	379	363	151	212	52.5	48.4	55.9
20-29	464	180	284	272	106	166	58.6	58.9	58.5
30-39	186	86	100	143	73	70	76.9	84.9	70.0
40-49	306	101	205	270	92	178	88.2	91.1	86.8
50-59	326	199	127	306	193	113	93.9	97.0	89.0
60-69	221	195	26	211	189	22	95.5	96.9	84.6
70 and over	32	28	4	28	24	4	87.5	85.7	100.0

Unpublished data, compiled by Ruth N. Crawford, R.N., United States Public Health Service, September, 1945.

TABLE 4

*Classification of 476 cases of reinfection type pulmonary tuberculosis, Colorado River Relocation Center, Poston, Arizona*

As of January 30, 1945

Active	
Minimal.....	40
Moderately advanced.....	36
Far advanced (including deceased).....	45
Total.....	121
Arrested	
Minimal.....	210
Moderately advanced.....	26
Far advanced.....	6
Total.....	272
Quiescent	
Minimal.....	23
Moderately advanced.....	8
Far advanced.....	4
Total.....	35
Questionable stability	
Total.....	48
Grand total.....	476

No estimation of the stability of lesions was attempted from the single survey films; 4.6 per cent of the more than 5,000 persons examined were found to harbor

roentgenographically demonstrable secondary type pulmonary tuberculosis. Only 0.9 per cent, however, showed far advanced disease.

Table 3 presents the results of tuberculin tests in 2,645 persons of all ages. Although the percentage of positive tests for all ages was 66.2 per cent, it is noteworthy that 90.3 per cent of persons over 30 years of age reacted to tuberculin and 37.7 per cent of children of 9 years or less were reactors.

*Third phase:* Table 4 shows the statistical summary of the incidence of reinfection type pulmonary tuberculosis among 8,652 persons, with subclassifications according to stability and extent of the disease process. It is adapted from a series of cumulative analyses made during the eight months of June, 1944 through January, 1945.

The table is simplified from the analysis of an active clinic following 784 persons; 50 cases in which the diagnosis of tuberculosis was unconfirmed, 44 in which it was abandoned and 214 cases otherwise irrelevant to this study were omitted from the table.

A total of 476 cases of reinfection type pulmonary tuberculosis was found among 8,652 persons X-rayed, a prevalence of 5.5 per cent. These 476 cases were kept under observation appropriate to the condition of the pulmonary lesion throughout the period of study or until the departure of the patient from Poston. Patients were routinely subjected to at least one reexamination by X-ray after a three to twelve months' interval. The only exceptions to this routine were persons over 40 years of age who exhibited fibrotic and calcified lesions of minimal extent. A diagnosis of active disease was not made on the unsupported evidence of a single roentgenogram.

Two hundred and four cases could not be classified as stable, there being either definite activity of disease or manifest focal instability without over-all change in the pathological picture. Thus only 272, or 57.1 per cent, of these cases were definitely arrested; 25.4 per cent had to be classified as frankly active, while 42.9 per cent were considered clinically significant.

#### DISCUSSION

*Statistical considerations:* Review of existing mortality figures of recent years (table 1) indicates a high tuberculosis death rate to have continued almost undiminished in Japan during a dramatic decrease in this country's mortality rates. The Japanese and Japanese-American population in California, while showing a tuberculosis death rate twice that for the California population, nevertheless shows a decrease in death rates comparable to that which the United States has experienced.

Study of chest roentgenograms of a group including persons applying to a general hospital for care, as well as those examined in an unselective survey, disclosed a prevalence of 5.5 per cent reinfection type tuberculosis. Routine survey of the unselected group alone revealed 4.6 per cent. In a thorough follow-up frankly active cases were found to comprise 25.4 per cent of all cases, although the diagnosis of activity was made conservatively.

These figures for the prevalence of reinfection type pulmonary tuberculosis

are substantially higher than those reported by Bass and Thompson (2). These workers based their findings on a survey in Tule Lake Relocation Center of 2,771 adult persons of Japanese ancestry whose pre-war residence and mode of life were comparable to those of our group. Using a Mantoux tuberculin test screening technique, they fluoroscoped 1,216 of the 1,233 reactors, or approximately 45 per cent of the total. A single dose of 1:10,000 (0.01 mg.) OT was used.

Our experience with tuberculin testing has been interesting in this connection. It was found that a substantial number of persons having a doubtful or negative reaction to 0.1 mg. of OT reacted positively to 1.0 mg. of OT. The smaller of these doses was ten times the strength of the single dose employed by Bass and Thompson.

Analysis of table 3 indicates that 90.3 per cent of persons over 30 years of age tested reacted to tuberculin. This sample tuberculin-testing (2,645 persons) led us to the conclusion that, as a screening procedure among the older age groups, the advantages of preliminary skin-testing, measured in time, labor and materials saved, were insufficient to merit continuance of the practice.

Hilleboe and Morgan (3) report that over a million workers in the United States Public Health Service were examined by portable photofluorographic units of the United States Public Health Service in 1942-1944. In this group, 1.5 per cent had X-ray evidence of reinfection type tuberculosis. Wassersug (4) quotes the U.S.P.H.S. figures as being representative of the general prevalence of the disease as determined by this technique. Yet this is one-third of the figure (4.6 per cent) obtained in the similarly conducted survey in Poston.

The California Tuberculosis and Health Association's (5) portable field unit took 29,092 films in six months in 1944. Tabulated results were based on X-ray readings alone. The photofluorograms were taken of persons in rural and urban communities in both northern and southern California; 2.9 per cent were considered to show actual or suspected tuberculosis. Activity of disease was not designated. This survey was geographically comparable to the Poston survey.

The 4.6 per cent prevalence of tuberculosis in the routine mass survey among persons of Japanese ancestry is statistically comparable to reported tuberculosis rates among patients admitted to clinics and hospitals throughout the nation.

Bloch and Tucker (6), fluoroscoping 15,000 consecutive patients in the University of Chicago Clinics, found 4.17 per cent to have tuberculous lesions of the reinfection type; 1.43 per cent were considered clinically important. The authors also report that, of 25,000 Negro out-patients examined at Provident Hospital, 4.0 per cent demonstrated secondary type tuberculosis and 2.6 per cent had clinically significant disease.

Seatchard and Duszynski (7) found 26 cases of clinically significant pulmonary tuberculosis among 725 new admissions to the Meyer Memorial Hospital in Buffalo, a prevalence of 3.6 per cent of active disease.

Hodges (8) reports that 7,841 successive patients were photofluorographed on admission to the University of Michigan Hospital, Ann Arbor, and that 9.3 per cent showed clinically significant intrathoracic disease; 1.5 per cent evidenced pulmonary tuberculosis of clinical significance.

*Clinical observations:* A number of interesting observations were made during the examination and treatment of patients.

Histories were uniformly unsatisfactory in the older generation. This was due in part perhaps to the unavoidable presence of an interpreter, but more particularly to the patient's ingrained reticence on the subject of tuberculosis. Histories were more helpful in cases of the American-born and educated. Often histories from these young people could not be completed in one interview, additional time being necessary to establish rapport. During these interviews, it was emphasized that a willingness to accept and, when necessary, to discuss one's tuberculosis was an integral step in the treatment of the disease. The patient was repeatedly admonished that his intelligent coöperation was superior to mere obedience, however slavish.

Percussion and auscultation of the chest are notoriously unremunerative in many cases. This was our experience. Furthermore, the language barrier added to the usual difficulties of examining the immobile chest of the emphysematous or senile patient. Inspection of the chest of the older man, however, often yielded a significant clinical finding, known as *okyu*, and peculiar, as far as we know, to the Japanese.

*Okyu* scars are circular, measuring 5 to 20 mm. in diameter, usually about 15 mm. They are the cicatrices of third degree burns inflicted by the burning of a small mound of incense, called *moxa*, on the skin, sometimes with a thin sheet of silver-foil interposed. This procedure is a Japanese form of counterirritation still widely practiced by the first generation Japanese of this country. (We have seen it performed once and have frequently seen the eschars of unhealed lesions.)

The position of these scars is determined by the site of the pain, the *moxa* being burned over the point of distress or in the paravertebral region over the root of the regional nerve supplying the painful area.

Many of the older men with chronic fibroid tuberculosis demonstrated a number of these scars on the shoulders or in the paravertebral area from the base of the neck to the base of the thorax. (Patients with peptic symptoms often manifest *okyu* scars in the epigastrium, and patients with peripheral neuritis may show the same lesions on the antero-lateral aspect of the lower leg.) Thus paravertebral scars were quickly recognized as good evidence of thoracic ills, long since forgotten or denied with a sense of shame.

*Differential diagnosis:* Acute pulmonary coccidioidomycosis is endemic in the American southwest, particularly in the San Joaquin Valley of California, the pre-war home of many of Poston's population (9). Recently an area of eastern California on the Arizona border, and hence not far from Poston, has been reported as another habitat of the infecting agent (10). Endemic areas within Arizona are located considerably further east. Because of these geographical factors and because of the occasional resemblance of the disease to tuberculosis, coccidioidin skin tests were done in all cases where any doubt of diagnosis existed.

Most of the cases of "Valley Fever" were of the acute type with symptoms lasting approximately six to ten weeks and with roentgenographic lesions healing

progressively to more or less complete resolution within a few months. A few cases, however, showed permanent parenchymal changes, not unlike fibrotic tuberculous lesions, and one case presented a residual basal cavitation for more than a year. This latter patient was subsequently inducted into the United States Army.

Serial roentgenograms taken at proper intervals served to differentiate acute and transitory pulmonary infiltrations from the tuberculous.

*Classification:* The *Diagnostic Standards and Classification of Tuberculosis*, 1940 edition, compiled and published by the National Tuberculosis Association, was used as a guide in classifying all cases. The limitations inherent in roentgenographic interpretation of pathological lesions in tuberculous lungs have been well demonstrated by Medlar, Pesquera and Ordway (11). The inadequacies of description of the minimal lesion within the terms of *Diagnostic Standards* have been pointed out by Reisner and Downes (12). These authors also reemphasize the complexities of evaluating the extent and dynamic status of the minimal lesion.

Our experience confirmed the unreliability of attempting to evaluate dynamic status from a single film. Therefore, in this study a diagnosis of active disease was not made on the evidence of one roentgenogram only. Serial films or clinical data or both supported the diagnosis in every case.

Variables of interpretation were minimized as far as possible by having all the roentgenograms showing tuberculous changes read or reviewed by one examiner. Technical qualities of the roentgenograms, although uniformly of a high standard, showed perhaps wider variations than usual since the Center's power supply was capricious and inconstant.

Laboratory facilities were not such as to justify heavy reliance on microscopic examinations of concentrated sputa or gastric contents. Cultures and guinea pig inoculations were not made. Consequently, some patients were classified as of "questionable stability" rather than quiescent, when clinical and roentgenological findings led us to believe that sputa might occasionally be positive although they had not been proved so.

While the limitations of present-day methods and those peculiar to this particular study were recognized, it was nonetheless felt that a fair evaluation of each case had been achieved. Repeated examinations, roentgenographic or clinical or both, over a significant period of time, decreased the subjective factor of film interpretation, neutralized the technical variations of roentgenograms and permitted observation of the patients' clinical course.

*Sociological aspects:* It is impossible to estimate the degree of psychic trauma attendant on the mass evacuation of 100,000 persons from their homes in time of war and under duress from hostile communities. Leighton (1) has emphasized the fact that Boston encompassed many of the basic types of stress which may threaten or assail an individual or a society. The effect there may have had on the course of tubercle in the group cannot be measured. We had no instance of expressed attribution of a patient's break-down to these pressures. However, it cannot be denied that the psychic stresses were indeed constant, sizable and unpredictable throughout both the evacuation and relocation periods.

During the study the strong social stigma borne by tuberculosis among the Japanese was noted. The existence of this stigma has been reported previously (2) and has been observed by every physician in the War Relocation Authority. Whereas a fear of tuberculosis and a reluctance to accept its diagnosis exist in the American population at large, this is based on the conviction that the disease is inherited and uniformly fatal (13). A social stigma, similar to that which attends syphilis, is not an integral part of phthisiophobia in this country, but pervades the Japanese culture here as well as in Japan.

No statistical data relating to factors affecting case rates and race susceptibility are presented. Nevertheless, contact histories suggest that the family's desire to conceal the presence of this disease in its midst is a major factor in disseminating tuberculosis through the younger generation.

#### SUMMARY

1. The findings of a two and one-half year study of pulmonary tuberculosis among 8,652 persons of Japanese ancestry, evacuated to a relocation centre in time of war, are presented and discussed.

2. The influence of the Japanese ignorance and superstition regarding tuberculosis is emphasized.

3. The educational value of a tuberculosis survey is considered.

4. A Japanese form of counterirritation is described and the significance of its aftermath as a physical sign considered.

#### CONCLUSIONS

1. Roentgenographic examination of 8,652 persons of Japanese ancestry disclosed 476 cases of reinfection type pulmonary tuberculosis, a prevalence of 5.5 per cent.

2. An unselective photofluorographic survey of the chests of over 5,000 Japanese and Japanese-Americans showed an incidence of 4.6 per cent.

3. Sample tuberculin testing of 2,645 persons yielded a prevalence of 90.3 per cent reactors in persons over 30 years of age and 66.2 per cent among all ages.

4. Of 476 cases of reinfection phase pulmonary tuberculosis, 43 per cent were considered clinically significant, while 25.4 per cent were frankly active; 57 per cent appeared to be cured or arrested.

5. The prevalence and activity rate for pulmonary tuberculosis in this group is significantly higher than that reported in comparable groups of Caucasian Americans. This conclusion is in accord with existing mortality statistics which indicate the tuberculosis death rate for California residents of Japanese ancestry to be twice that for the California population as a whole.

#### CONCLUSIONES

1. El examen roentgenográfico de 8,652 descendientes de japoneses reveló 476 casos de tuberculosis pulmonar tipo reinfección, o sea un coeficiente de 5.5 por ciento.

2. Un estudio fotorroentgenográfico del tórax de más de 5,000 japoneses y japoneses-estadounidenses tomados al azar reveló un coeficiente de 4.6 por ciento.



3. La comprobación con tuberculina de una muestra de 2,645 personas dió un coeficiente de 90.3 por ciento de reactores en las de más de 30 años de edad y 66.2 por ciento a todas las edades.

4. De 476 casos de tuberculosis pulmonar en la fase de reinfección, a 43 por ciento se les consideró de importancia clínica, en tanto que 25.4 por ciento eran francamente activos, y 57 por ciento parecían hallarse curados o estacionados.

5. Los coeficientes de incidencia y de actividad de la tuberculosis pulmonar en este grupo son decididamente más altos que los comunicados para grupos comparables de estadounidenses de raza caucásica. Esta conclusión conviene con las actuales estadísticas de mortalidad, pues éstas indican que la mortalidad tuberculosa en los residentes de California de ascendencia japonesa es el doble que en la población de California en conjunto.

The author wishes to express acknowledgment to Dr. A. Pressman, National Medical Consultant for the War Relocation Authority, and Principal Medical Officer at Poston during most of the period of this study, for his encouragement and assistance.

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# TUBERCULOSIS IN THE SAN BLAS INDIANS OF PANAMA

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It is generally said that the American Indian has a high rate of tuberculosis infection and little resistance to the disease. However, the identification of a pure Indian is usually difficult; environmental factors must be evaluated, and contacts with other peoples cannot always be traced. The San Blas Indians are a "pure," isolated, aboriginal population of Panama. Recently, many of them were employed by the Army of the United States, thus exposing them to "civilization." It is with the consideration of these factors that this study is presented.

Moll (1) believes that tuberculosis may not have existed in pre-Columbian America and Hrdlička (2) showed that tuberculosis was more common in those North American Indians who had more frequent contacts with the white man. Long (3) states that the tuberculosis mortality of Indians in the United States is three or four times as high as in Negroes and nine to twelve times as high as in whites. Similar observations have been made by Dublin (4) and Townsend (5) in the States and by Walton (6) in Manitoba, Canada. In Mexico, however, Alarcón (7) was unable to find evidence of increased incidence or severity in Indians and mestizos other than could be accounted for by poverty, bad housing, poor education and dangerous trades. Francis (8), in British Guiana, published morbidity figures that are lower in the aboriginal Indians than in the Negroes, Portuguese and Chinese.

## SOURCE OF MATERIAL

This report is based on the findings in 604 San Blas Indians processed in the Central Labor Office of the Canal Zone from October 1, 1944 to December 19, 1945.

The war created a shortage of shipping and many Indians, who were dependent on their coconut trading for many of the articles they had learned to use, left the islands to seek work on the mainland. A great shortage of labor existed in the Canal Zone and the Republic of Panama, and Indians were readily hired by the Army. They were adaptable, cleanly in their habits and excellent workers in kitchens and hospitals on army posts.

As many were handling food and in almost constant association with soldiers, it was decided to make 14 by 17 inch chest roentgenograms on all San Blas Indians before employment. Stereoscopic and apical views were used when indicated. Thus each Indian received (1) a physical examination, (2) a determination of height and weight, (3) a Kahn test and (4) an urinalysis. Other studies were made when indicated. Previously, all food handlers in the Canal Zone had been examined in this manner, and among these were 4 San Blas Indians with pulmonary tuberculosis who have been included in this report.

The keeping of records of the Indians was difficult. Partly because Indian

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names like *Manijupitguina* are cumbersome, and partly because of a superstition that revealing one's true name is unlucky, the Indians use North American or Spanish names which they change at will. Thus, 21 Indians used the name Tony Morris at one time or another. When possible, finger prints were used to identify Indians. The ages given by the people are only approximations, short periods being counted by "moons" and longer periods being guessed, with some degree of accuracy.

#### ANTHROPOLOGICAL CONSIDERATIONS

Remarks concerning environmental factors are based on a visit to the San Blas Islands.

The Cuna or Tule Indians are one of the aboriginal peoples living in eastern Panama. The Cunas live in isolated groups on the mainland and on hundreds of reefs and islands strung along the Caribbean coast seventy-five miles from the Canal Zone and south to the Colombian border. These islands were first visited by Rodrigo de Bastidos in 1501 and two years later by Columbus on his ill-fated fourth voyage. At that time the islands were not inhabited, but the Cunas occupied the adjoining mainland. Columbus contacted the Cunas, but had little time to trade as his ships were riddled with boring worms. Before he left he named the islands for Saint Blasius. Later the Cunas were driven from the mainland to the islands by the Spanish as well as by other hostile Indians. According to the local custom, the Indians inhabiting these islands became known as the San Blas Indians.

One of the earliest accounts of the Cuna Indians is that of Lionel Wafer, surgeon to a party of British buccaneers. In 1681 he was captured by the Cunas after injuring his knee in a powder explosion. The Cunas, although unfriendly, treated his wound with a poultice of chewed herbs and plantain leaf. He later overcame their hostility by showing them how to let blood from a vein rather than by shooting small arrows into the patient. His success in minor surgery was so great that he finally received an offer of a chief's daughter in marriage. Wafer (9) wrote that the Cuna men were "straight and clean limbed, big-boned, full breasted, and handsomely shaped . . . I never saw among them a crooked or deformed person." He also noted the presence of albinos or "moon children."

The Indians are very much as Wafer first described them—short (average height 50.5 inches), red-brown in color, with large barrel-shaped chests. Their heads are not low and are extremely brachiocephalic (cephalic index 88). Their arms are relatively long with small, delicate, child-like hands; their legs are short with well spread feet and great malar development. Their eyes are monophthalm and blue long, straight and black, giving them an oriental appearance. They are certainly not of a "physical habitus." (Figure 1.)

The Cuna group has been variously described as Mayan, Carib and Arawak. However, the language and culture is Chibchan, that Indian culture which centers about the Boyacá plateau of Colombia. Cuna men do not resemble Chibchan men in the least; and it is difficult to speak of the Cuna as members of

are disguised by ear-rings, nose-rings, clothing, and paint on occasion. There has never been interbreeding with other peoples, except for a few children who were sired by a Panamanian police force stationed on the islands for a short time. Both the mixed children and their fathers were killed in a miniature revolution. The appearance of a Cuna Indian is so distinctive that he can readily be recognized.

Food is obtained by fishing with spears, gathering coconuts and by farming small clearings on the Panamanian mainland. Whatever trading is done with the outside world depends on the coconut. Their large huts, built here and



FIG. 1. A young adult San Blas Indian

there on the reefs and islands, are made of cane with thatched roofs. Several islands are more densely populated, with huts jutting against each other and narrow streets passing through the villages. Sanitation is no problem, for all refuse is simply thrown into the sea.

#### HEALTH OF THE SAN BLAS INDIANS

The San Blas enjoy good health. The 604 Indians included in this study had relatively few abnormal physical findings. The commonest abnormality was a pterygium encroaching on the cornea and resulting in poor vision. Visual loss was more severe in the near-albinos who have little protection from the tropical

sun. Only 6 San Blas Indians had palpable spleens; while 3 of 9 Bayanos, another Cuna group from the mainland, had spleens reaching to the umbilicus. Malaria is rare in the San Blas islands because the continuous winds prevent the flight of the mosquito. Tonsils were large and teeth nearly perfect. Caries was rarely seen and then usually in those who had lived away from the islands. Tachycardia, functional murmurs and congenital heart disease were occasionally observed. There was only one hernia in the group. Only 2 of those examined were females, for the women rarely leave the islands.

Several interesting studies have been made recently on the San Blas Indians. In 1941 Kumm and Crawford (10) examined blood specimens for yellow fever antibodies and found 4.6 per cent positive by mouse protection tests. Kean (11) reported a total absence of hypertension in these Indians. In 1932 there was an epidemic of alastrim in the islands. In 1942 there was an epidemic of *rubeola* with many pulmonary complications and a high fatality rate.

#### RESULTS OF ROENTGENOGRAPHIC STUDIES

Evidence of pulmonary tuberculosis other than calcified primary lesions was found in 13 of 601 roentgenograms, a prevalence of 2.2 per cent. Four other Indians with pulmonary tuberculosis were found among those already employed as food handlers. Pertinent data pertaining to this group of 17 patients are shown in table 1. Calcified primary lesions were present in approximately 14 per cent of the films.

The following conditions were noted in the 17 patients listed in table 1:

Evidence of healing	5
Cavitation	9
Consolidation	2
Minimal lesions	5
Bilateral lesions	5

Thus, the majority have moderate or wide-spread tuberculosis. This is contrary to the usual findings in surveys where the lesions discovered are for the most part minimal. However, the evidence of healing in 5 (29 per cent) of the patients and the presence of calcified primary lesions in approximately 14 per cent of the films show a greater resistance and tendency to healing than might be expected.

#### TUBERCULIN TESTING

It is of interest to study Purified Protein Derivative tuberculin by the method of Kohn (12) as employed on 37 Indians. A larger number of tuberculin tests were performed for comparative purposes. They are people with such varying degrees of tuberculosis that it is difficult to draw conclusions from the results of the tests. The results of the tests are shown in table 2. Although the results are not statistically significant, the results are of interest. It is interesting to find that the results of the tests are not statistically significant, but the results are of interest.

TABLE 1

*Data concerning Indians with lesions of pulmonary tuberculosis other than healed primary lesions*

AGE	YEAR OF EMPLOYMENT	HEIGHT	WEIGHT	GRAPHIC FINDINGS
		<i>inches</i>	<i>lbs.</i>	
1. 21		59½	108	Far advanced bilateral pulmonary tuberculosis with cavitation.
2. 17	1943	60½	108	Parenchymal infiltration of the upper lobe of the left lung.
3. 23		61	120	Parenchymal infiltration with a small cavity in the apex and first interspace of the upper lobe of the right lung.
4. 21	1941	63	120	Extensive infiltration with a small cavity in the upper lobe of the left lung and an area of infiltration at the level of the second interspace on the right.
5. 16		60½	110	Extensive infiltration in the upper lobes of both lungs with cavitation at the level of the second rib on the left and first rib on the right.
6. 22	1941	62½	120	Minimal tuberculosis involving the apex of the left lung.
7. 22	1943	59	108	Consolidation and cavitation of the upper lobe of the left lung.
8. 22		60½	113	Exudative lesion and a large cavity in the upper lobe of the right lung.
9. 50	1941	55½	100	Chronic fibroid lesion at the level of the first interspace on the right. Minimal tuberculosis.
10. 19		57	110	Exudative lesion of the upper lobe of the left lung. Moderately advanced tuberculosis.
11. 29	1941	63	152	Fibrous lesion at the level of the right third rib. Minimal tuberculosis, activity undetermined.
12. 30	1941	62½	124	Tuberculous pneumonia of the lower half of the upper lobe of the right lung.
13. 23		61	125	Infiltration and cavitation of the apex and first interspace on the right.
14. 19	1944	59	115	Fibrous lesion of the upper lobe of the right lung, possibly inactive.
15. 15		58½	90	Infiltrative densities of the apex of the left lung with extension to the hilus.
16. 22	1943	58½	101	Parenchymal infiltration throughout the upper lobe of the right lung with two cavities, and mottling in the left mid-lung field.
17. 18	1944	62½	140	Parenchymal infiltration in the second and third interspaces and a cavity at the level of the third rib in the left lung. Parenchymal infiltration at the level of the third rib in the right lung.

Forty-six per cent of these 37 Indians had positive reactions, most of them being severe. Second-strength tests were not made. No conclusion can be drawn from such a small number of tests.

## AUTOPSY OF A SAN BLAS INDIAN WITH TUBERCULOSIS

A San Blas Indian came to autopsy at the Board of Health Laboratory of the Canal Zone. He was a 22 year old employee who left his work one day and reported to the Margarita Hospital with the complaints of headache and back deformity. He had been working for one year and his work had always been considered satisfactory. A history was not obtainable because of language difficulties. The patient rapidly became comatose and died four days after admission to the hospital. At autopsy there were two caseous and partly calcified pulmonary lesions, miliary pulmonary lesions, tuberculous osteomyelitis of the first three lumbar vertebrae, and probably a tuberculous meningitis. These findings may also serve to show the fulminating character of the disease at times and the typical stoicism of the Indian.

## COMMENT

There was no clearly demonstrated increase in the incidence of pulmonary tuberculosis after employment away from the islands. As noted in table 1, 10 (60 per cent) of the Indians with pulmonary tuberculosis had records of previous employment. Approximately 60 per cent of the total 601 Indians examined had previous employment.

There was little outward sign of the disease in those with pulmonary lesions, and often they were of better than average weight. In figure 2 the weights of those Indians with lesions are noted on a graph of average height-weight obtained from the records of 250 Indians. It would suggest a disease process so rapid that there is little time for wasting.

The relatively large number of Indians with fulminating lesions may not be a racial phenomenon, but one of climate. Strong (12) believes that tuberculosis is more severe in tropical regions, particularly in regions located at sea level and having a high relative humidity. These conditions are found at their extreme in Panama, and most physicians here agree that patients with tuberculosis do poorly, irrespective of race.

It is possible that the incidence of pulmonary tuberculosis may be higher than this study indicates. Indians who are ill may not apply for work and those who become ill may return to their homes without their disease being reported.

The greatest danger for the Indian lies in the cities of Panama where the rate of infection is high. There is little exposure to tuberculosis on army posts. In general, military personnel are in good health and have had roentgenographic studies of their lungs before entering the Army.

The Indian shows no emotion when told that he has tuberculosis, although he seems to understand its importance. Many of them know the disease by the Spanish word *tuberculosis*. Sometimes, on questioning, an Indian will relate how he has caused an entire family—husband, wife and child to die from the disease. In some instances the risk of infection is recognized from his fellows on the island and the probability of the rate of infection.

The Indian soldier employed at all four United States tuberculosis centers for

hospitals in the Canal Zone. He will not enter a hospital in the Republic of Panama, for his hostility to the Latin is almost hereditary and dates back to the days of the Conquistadores. He returns to the islands and becomes a patient of the Indian medicine man. Patient and medicine man go to the mountains on the Panamanian mainland for a week's stay and the sick man is plied with native drugs. He returns home where he may spread the infection, recover or die.

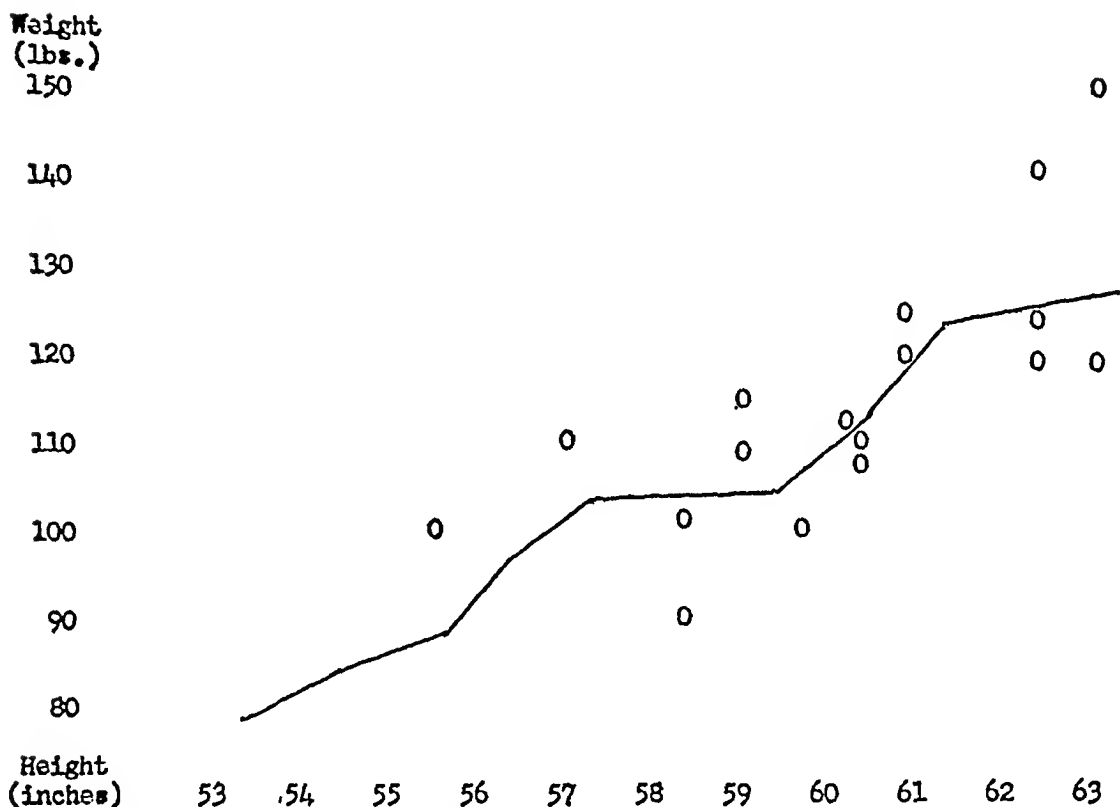


FIG. 2. Height-weight graph of San Blas Indians. The O's indicate Indians with pulmonary tuberculosis

#### SUMMARY

Many San Blas Indians, members of a "pure," isolated, aboriginal population of Panama, were recently hired by the Army of the United States, thus exposing them to "civilization." They were given complete physical examinations and roentgenograms of their chests prior to employment.

In 604 consecutive roentgenograms, lesions of pulmonary tuberculosis other than calcified primary lesions were found in 13, or 2.2 per cent. Of 17 Indians with pulmonary tuberculosis, 5 showed evidence of healing and 10 were of a fulminating character. Calcified primary lesions were present in approximately



14 per cent. The incidence of pulmonary tuberculosis did not appear to be significantly greater in those who had previously been employed away from their native islands.

#### SUMARIO

Muchos indios de San Blas, miembros de una población aborigen, aislada, "pura" de Panamá, fueron empleados recientemente por el Ejército de los Estados Unidos, quedando así expuestos a la "civilización."

Antes de darles empleo, fueron objeto de completos exámenes físicos y radiografías torácicas. Entre 604 radiografías consecutivas, encontráronse en 13 (2.2 por ciento) lesiones de tuberculosis pulmonar, distintas de las lesiones primarias calcificadas. De 17 indios que padecían de tuberculosis pulmonar, 5 revelaban signos de cicatrización y en 10 la enfermedad era de naturaleza fulminante. Aproximadamente en 14 por ciento había lesiones primarias calcificadas. La incidencia de la tuberculosis pulmonar aparentemente no alcanzaba mayor importancia en los que habían estado empleados fuera de sus islas, que en los otros.

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# TUBERCULOSIS IN LIBERATED EUROPEAN POLITICAL PRISONERS OF WAR

Pathological Study of 87 Fatal Cases

CHARLES P. LARSON<sup>1, 2</sup>

This report should be of interest and value because of the large number of autopsies performed on a group of men who not only had tuberculosis but who also showed the concomitant effects of severe starvation with avitaminosis.

During the months of December, 1944 and January, 1945 approximately 300 Russian and Italian liberated prisoners of war were admitted to the 50th (US) General Hospital for treatment. The clinical diagnosis on the vast majority of these cases was pulmonary tuberculosis. By the 1st of June, 1945, 90 of these patients had died and complete autopsies were performed upon them. In 87 of these cases tuberculosis was the primary cause of death. The following pathological summary is based upon these cases.

Seventy-five of those dying were Russians and 12 were Italians. The average number of days of hospitalization in this hospital was thirty-six. However, this figure does not show the fact that a high percentage of these patients died within a few days after admission (see graph 1). The average age was 31 years.

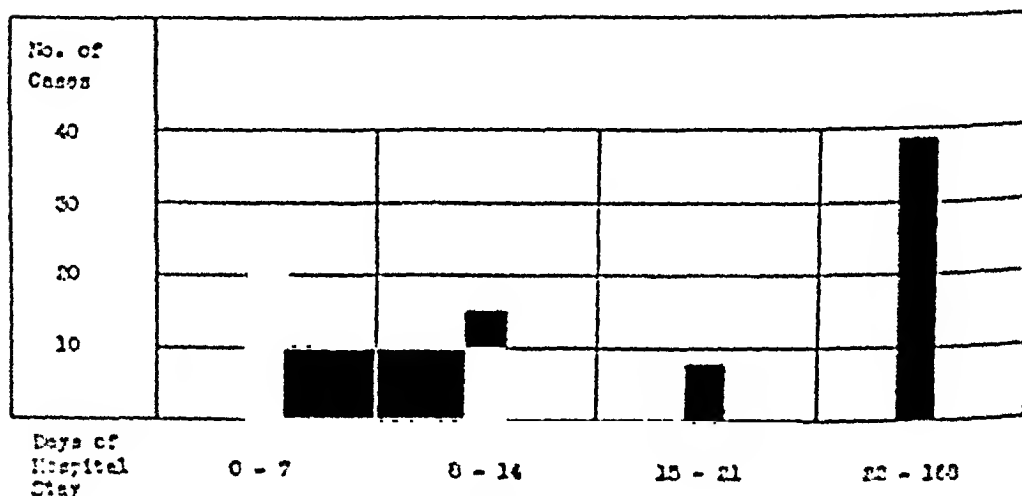
A clinical history as regards the duration of the illness was obtained in only 40 cases. The average duration of illness before death was 11.6 months. Actually this figure should be much higher because no attempt had been made by the Germans to make an early diagnosis of tuberculosis in this class of prisoners of war. No hospitalization or treatment was instituted by the Germans until the disease was so far advanced and the patients so seriously ill that they had become unable to carry out manual labor duties. In this regard it should be remarked that the living conditions of these patients while under German authority were deplorable. Approximately 100 men were crowded into one small wooden barracks, 60 feet long by 17 feet wide, with practically no ventilation. They were forced to sleep on wooden ledges covered with straw and lay side by side with no separating partitions. These ledges were double-decked with a space of only 2 feet between the upper and lower decks. There were two parallel rows of these double-deck ledges, one on each side of the room, with an aisle 3 feet wide down the centre. Many of these barracks had no flooring. Latrine and hygienic facilities were notably inadequate. Only one small hand towel was issued to each prisoner approximately once every three months. Blankets were inadequate in number, averaging only one per person even for the winter months. Clothes were of a very poor grade of cotton-wool mixture and no overcoats were issued. Many of the men had no shoes when they were liberated by the Americans. As can be deduced, these living condi-

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tions were extremely favorable for the spread of tuberculosis, or in fact any communicable disease. If one person in a barracks had active tuberculosis, all the others were subjected to a maximal exposure. As a result, there was a large percentage of cases of recent tuberculosis, which was proved by autopsies of this series.<sup>2</sup>

Fifty-four patients had chest X-ray films and a total of 7 discrepancies were noted in the X-ray reports when compared with the anatomical diagnosis at the time of autopsy. This yields an apparent diagnostic error of 13 per cent. In 3 cases the pulmonary tuberculous lesions were not observed in the films, but those which were missed were small and recent lesions. In 2 other cases military tuberculosis was not observed but in one of these cases the chest film was taken six weeks before death, so the lesions may not have been present at the time the film was made. In one case the radiological diagnosis was military tubercu-



GRAPH 1. Days of hospitalization before death

los, whereas, at autopsy, a recent disseminated bronchogenic fibromyxoid tuberculous was found. The seventh radiological discrepancy was in a patient who had military tuberculosis at the time of autopsy, whereas the radiological diagnosis was recent bilateral fibromyxoid pulmonary tuberculosis. It must be added that many of the chest films were taken with a portable machine and under unfavorable conditions.

Fifty-four cases had one or more sputum examinations for the presence of tubercle bacilli. In 6 of these cases no tubercle bacilli were found, which yields an apparent laboratory error of 10.6 per cent. However, in 4 of these cases in which tubercle bacilli were not demonstrated, only a single sputum specimen was examined.

From these figures it can be observed that the percentage of apparent diag-

<sup>2</sup> The percentage of tuberculous persons in the barracks at the temporary detention camp at Fort Belvoir, Fort Belvoir, Investigating Team, 1940-1941.

nostic error of the laboratory and radiological departments were about equal. In only 2 cases (both military tuberculosis) was there a failure to make a positive diagnosis by one or the other of these departments. More than one examination by either of these departments would have probably increased the number of positive diagnoses to 100 per cent.

In 30 cases one or more blood sedimentation rates were determined and the average sedimentation rate for all of these was very high, being 52 mm. in sixty minutes. On 36 cases complete blood counts were made. The average leucocyte count was 11,000 and the average hemoglobin content was 8.8 g. The average of the differential blood counts showed a slight lymphocytosis but not enough to have been of diagnostic significance.

The average height of these individuals was 168 cm. (5 feet, 7 inches), and the average weight was 106 pounds. Since the normal average weight for men 31 years of age and 5 feet, 7 inches tall is 149 pounds (1), some opinion as to the extreme degree of emaciation of the majority of them can be formed. Judging emaciation on a basis of complete absence of subcutaneous fat, 72 cases, or 82.8 per cent, were severely emaciated. The average height of those patients who were classified as emaciated was 168 cm. (5 feet, 7 inches) and the average weight was 100.3 pounds; therefore these men were each approximately 50 pounds underweight, which represented a loss of one-third of the body weight from the normal average. In addition, 80 cases, or 91.9 per cent, presented evidence of generalized muscular atrophy.

This degree of emaciation could not be accounted for solely as a result of the tuberculosis. An investigation was made of the daily average diet which was provided for these men while they were in German concentration camps. For the three months immediately preceding liberation the diet supplied was much poorer than before. Briefly, the average diet for the months of September, October and November, 1944 was as follows:

*Breakfast:* A cup of weak tea or *Ersatz* coffee with a small slice (approximately 75 g.) of black bread. Often nothing but the cup of tea was served.

*Dinner:* The usual food was approximately 300 to 350 cc. of a thin watery soup, prepared from potatoes and turnips with only occasionally a small amount of meat extract added for flavoring. The potatoes and turnips used in preparing these soups were of the poorest quality, often spoiled. The skins and all were utilized.

*Supper:* The usual meal consisted of another 300 cc. of thin potato soup and the daily ration of 250 g. of German black bread. This bread was of the poorest quality, often very dry and mouldy. Once or twice a week a small ration of poor quality sausage or cooked horsemeat was added to the evening meal. No supplemental minerals or vitamins were provided. However, many prisoners would daily eat grass and certain other edible greens that they were able to find growing in the vicinity.

The total average daily caloric intake was approximately 1,000 calories. Since the average daily caloric requirement for a man of this average size, performing twelve hours of manual labor, is approximately 3,750 calories, the cause of the extreme degree of emaciation is obvious. Of the 87 cases reported in this series, 15 were not so markedly emaciated, which can be explained by



TABLE 1  
*Incidence of organ tuberculosis in 87 cases*

ORGAN	NUMBER OF CASES INVOLVED	PER CENT
Pulmonary		
A. Right lung (Total).....	86	98.8
1. Recent tuberculosis.....	28	32.2
2. Old tuberculosis.....	58	66.6
B. Left lung (Total).....	85	97.7
1. Recent tuberculosis.....	22	25.3
2. Old tuberculosis.....	63	72.4
Pleura		
A. Pleurisy (right) (Total).....	76	87.3
1. Productive pleurisy.....	62	71.2
2. Exudative pleurisy (empyema)	14	16.1
B. Pleurisy (left) (Total).....	78	89.6
1. Productive pleurisy.....	58	66.6
2. Exudative pleurisy (empyema)	20	23.0
Lymph nodes		
A. Thoracic.....	79	90.8
B. Abdominal.....	54	62.0
Intestine.....	47	54.0
Peritoneum.....	16	18.4
Spleen (Total).....	58	66.7
A. Gross involvement (caseous)....	16	18.4
B. Microscopic involvement (focal)	42	48.3
Liver (Total).....	64	73.5
A. Gross involvement (caseous)....	7	8.0
B. Microscopic involvement (focal).	57	65.5
Kidneys (Total).....	14	16.1
A. Gross involvement (caseous)....	6	6.9
B. Microscopic involvement (focal).	8	9.2
Miliary tuberculosis.....	3	3.4
Bones.....	9	10.3
Pericardium.....	7	8.0
Skin.....	5	5.7
Genital.....	1	1.1
Esophagus.....	1	1.1
Anus.....	2	2.2

of the productive type, the vast majority of which, on microscopic study, proved to be of tuberculous origin.

In 79 cases, or 99.8 per cent, tuberculosis of the thoracic lymph nodes was verified microscopically and 51 cases, or 62 per cent, showed a similar finding in the abdominal lymph nodes.

Tuberculous enteritis of the small intestine was found in 47 cases, or 51 per cent. Most of these cases also showed some smaller lesions in the large intestine, particularly the cecum. Tuberculous peritonitis was observed in only 16 cases, or 18.4 per cent.

A very large number, 58 cases, or 66.7 per cent, showed focal splenic tuberculosis, of which 16, or 18.4 per cent, were observed grossly and were of the caseous type, while the balance, 42 cases, were of the focal type observed only in the histological sections. The liver was involved in 64 cases, or 73.5 per cent. Of these, only 7, or 8 per cent, were seen grossly and were of the caseous type. There were fewer cases of renal involvement: only 14, or 16.1 per cent, 6 of which were of the gross caseous type.

Only 3 cases, or 3.4 per cent, in this series showed typical generalized miliary involvement. Bone tuberculosis was observed in only 9 cases, or 10.3 per cent, but this figure is probably much too low because all the vertebrae and joints were not thoroughly explored. Incidental foci of tuberculosis in other organs included one case of involvement of the esophagus; 7 cases of pericarditis; 2 of the lung; 2 cases of pleuritis; one case with prostate and epididymal involvement; and 5 with cutaneous or subcutaneous tuberculosis. The only adrenal involvement noted was focal microscopic nodules in 2 cases, but in these the amount of parenchymal loss was so slight that no symptoms of adrenal insufficiency could have resulted. It is interesting to note here that the clinical diagnosis which was made on several of the patients dying within a few days of admission was Addison's disease. The autopsies revealed that the extreme emaciation and severe skin pigmentation were produced by factors other than a lesion in sufficiency.

In practically all instances, there were varying degrees of pulmonary anthracosis, but in only one instance was there a demonstrable silicosis.

Acute inflammation, using the spleen as an index, was observed in 8 instances, or 9.2 per cent.

In 10 cases marked unilateral edema of the extremities was observed. In only 2 of these cases could the unilateral edema be attributed to venous or arterial thrombosis. In the other 8 cases, the only observable cause of the unilateral edema was the extensive thrombotic tuberculous involvement of the regional lymph nodes. In spite of the fact that there has been an accumulation of fluid in the lymphatic spaces of the extremities, an extremity could be bled, the lymphatic spaces failed to distend either grossly or microscopically, and the lymphatic vessels of the extremity failed to reveal the tuberculous thrombotic changes. It would be reasonable to assume that the lymphatic system of the extremities

In addition to the tuberculous lesions observed in this series included 2 cases of toxemia, 1 case of pyelitis, 1 case of pyelonephritis, 1 case of bronchitis, 1 case of

with true parenchymal fusion; and 8 of complete pulmonary collapse secondary to tuberculous empyema. There were 4 cases of ulcerative colitis produced by bacteriologically proved bacillary dysentery.

The microscopic study of the livers in this series proved to be particularly interesting. In 54 cases, or 62 per cent, there was a very marked fatty infiltration. No pancreatic lesions were noted. MacCallum (3) states, "The consumptive wastes away and becomes anaemic, the metabolism of fat is disturbed so that it accumulates in the liver, and there are general evidences of poisoning to which the ancient term 'cachexia' applies." From my studies of this series of cases, it appears as though the fatty infiltration of the liver was more likely produced by the extreme malnutrition where the body was utilizing its own fat as a source of energy for a long period of time. This reasoning is substantiated by the fact that in those cases remaining alive in this hospital, for a period of two weeks or longer, under adequate diets, the fatty infiltration of the liver was either not present or less severe, whereas the tuberculosis was unimproved. In 75 cases, or 86.2 per cent, there was a parenchymatous or fatty degeneration of the liver cells. This finding could very well have been secondary to the terminal tuberculous "cachectic" state. In 14, or 16.1 per cent, of the livers, there was also an exudative cholangitis which in some instances extended into the parenchyma so that it could have been considered as a hepatitis. These were microscopically indistinguishable from the cases we now know and call "infectious hepatitis," but if any of these individuals had symptoms of this disease during life they were masked by the more severe condition, namely, the tuberculosis.

#### SUMMARY

The pathological lesions found at autopsy on 87 cases of Russian and Italian political prisoners of war with tuberculosis have been classified.

The concomitant effects of severe starvation with avitaminosis have been discussed. The dietary and living conditions of these prisoners under German military control were described together with the relationship of these to the development of the lesions found at autopsy.

#### SUMARIO

Clasificanse las lesiones patológicas descubiertas en la autopsia en 87 casos de tuberculosis en rusos e italianos que eran prisioneros políticos de guerra.

Discútense los efectos concomitantes de la inanición intensa acompañada de avitaminosis. Descríbense las condiciones de vida y de alimentación de estos prisioneros mientras se encontraban en manos de los alemanes y la relación de aquellas con la aparición de las lesiones descubiertas en la autopsia.

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# THE EFFECT ON TUBERCULOSIS MORBIDITY OF A COMPLETE COMMUNITY SURVEY WITH HOSPITALIZATION OF ALL ACTIVE CASES

ROBERTS DAVIES<sup>1</sup>

The development of photoroentgenological methods has given a great impetus to the use of mass surveys for tuberculosis case-finding. Such surveys have been largely confined to selected groups, especially industrial workers, and only a few complete community surveys have been reported. There are impressive reasons for such a selection. Community surveys are comparatively difficult to organize and to conduct and are therefore relatively expensive and time-consuming. Moreover, by the selection of high incidence groups, such as old age pensioners and unskilled laborers, one finds a higher percentage of active tuberculosis.

However, the practicability of complete community examinations has been demonstrated in several areas, both in the United States and elsewhere. From a theoretical viewpoint, such surveys, when combined with isolation and treatment of all active cases, would seem to offer an ideal method of tuberculosis control, at least in self-contained communities with little immigration. The complete community survey enables us to remove all or almost all the active cases of tuberculosis from a community at one time and thus to stop, for a period, the spread of the infection. If most cases of clinical, so-called adult type tuberculosis are due to reactivation of a latent primary infection, one would expect the beneficial effects of such a community cleansing to appear only after an interval of perhaps ten years or longer and then only if the survey had been repeated, perhaps at yearly intervals, to weed out the new cases of endogenous reinfection as they appeared. On the other hand, if most cases of clinical tuberculosis in adults are the result of recent exogenous infection, one would expect a rather sharp drop in morbidity to follow promptly after a successful community examination. In the latter eventuality, the complete community survey might well be the cheapest as well as the most effective method of tuberculosis control, as measured by the improvement in morbidity and mortality achieved by a given expenditure of time and money.

Because of the interest and importance of such considerations we have undertaken to study the results on tuberculosis morbidity of a complete community survey which we made of a rural township in St. Louis County in 1937. We have compared the incidence of new cases of tuberculosis during the seven-year period following the survey (1938 to 1944 inclusive) to the incidence that would have been anticipated if no survey had been made. We have chosen the incidence of new cases for study, rather than sanatorium admissions or tuberculosis deaths, because we feel it reflects most accurately the current status of tuberculosis control.

<sup>1</sup> Nopeming Sanatorium, Nopeming, Minnesota.

## MATERIAL AND ANALYSIS

The community was selected for survey because of a shocking prevalence of tuberculosis. Before the survey was begun, 21 persons (5.6 per cent) out of population of 376 were known to have definite adult-type pulmonary tuberculosis. Nine of these people were at that time patients at the sanatorium with active disease, while the remaining 12 cases were classified as arrested. The average annual tuberculosis death rate for the preceding fifteen years had been 200 per 100,000.

A house-to-house canvass was made and Mantoux tests with PPD were given to everybody. The usual first strength dose of .000,02 mg. was used for the first test and all nonreactors were retested with .002,5 mg. All reactors to either test were examined with single 14 x 17" X-ray films of the chest taken at Nopeming Sanatorium.

Of the 367 people in the community (not counting the 9 patients in the sanatorium), 301 (82 per cent) were adequately examined. Forty showed evidence of adult type tuberculosis, of which 32 were apparently inactive and 8 were definitely active. Of the 8 active cases, 2 were minimal, 5 were moderately advanced and one was far advanced. All 8 were admitted to the sanatorium and all were eventually discharged with arrested disease. All cases, active or inactive, were listed for permanent follow-up by the sanatorium outpatient department.

To calculate the number of new cases of tuberculosis that would have been anticipated if no survey had been made, we have determined the incidence of new cases in the seven-year period preceding the survey (1930 to 1936 inclusive) and corrected the incidence for the change in age and sex distribution in the community in the seven years following the survey and for the improvement in tuberculosis experience which occurred throughout the county as measured by the fall in the mortality rate. The usual statistical methods for the study of trends were not applicable because no trend was evident in the incidence of cases before 1937.

At no time since 1937 has the general antituberculosis program of this county been prosecuted in this community any more vigorously than in any other part of the county. We are unable to think of any factor other than the change in population and the 1937 survey which might have resulted in a better tuberculosis experience in this township than in the county as a whole in the years 1938 through 1944.

To find the incidence of cases of tuberculosis in the period 1930 to 1936 we have searched the files of Nopeming Sanatorium both for outpatients and sanatorium admissions from this township and have searched the reports of cases and of deaths furnished by both the St. Louis County Health Department and the Minnesota State Health Department. During the 1937 survey we asked each person examined for a history of contact with tuberculosis and we have cross-checked our files for the names of all persons so listed as contacts. In each case all available records were reviewed and no case was included unless the evidence of active tuberculosis was convincing. All cases were tabulated by sex, age at onset, year of onset and extent of disease. The year of onset was determined by the first suggestion of active tuberculosis, such as the onset of pulmonary symptoms which

persisted or increased until the diagnosis was made. Cases in which the year of onset could not reasonably be determined from the available records were not included, since their onset may have been before 1930. Cases of legal residents of the township who were first reported as having tuberculosis after leaving the township and living elsewhere, as in the state mental hospitals, were also excluded, since exposure after leaving the township may have been responsible for their disease. We found 19 cases of tuberculosis which satisfied all requirements for inclusion in the list of cases with onset during the years 1930 through 1936. All of these cases were diagnosed in 1937 or before. Two of them were minimal, one complicated by tuberculosis of the spine; 11 were moderately advanced; and 6 were far advanced. Six have died, 4 from tuberculosis and 2 from apparently nontuberculous disease.

To find the incidence of tuberculosis in the years 1938 to 1944 inclusive, we made a similar search of all available records, using the same criteria and, in addition, in the summer of 1944 we again made a complete community survey of the township with the St. Louis County mobile X-ray unit. By this time the population had shrunk to 294. The mobile X-ray unit examined 257 (87.4 percent) with 4 x 5" photofluorograms and of the remaining 37 persons, 9 had had recent 14 x 17" chest X-ray films. No new case of tuberculosis was discovered, but one ex-sanatorium patient was found to have reactivated his disease.

There are only 2 persons who can possibly be considered to have developed tuberculosis in this community in the years 1938 to 1944 inclusive. One is a man who was living in Oregon at the time of the 1937 survey. He returned to the township in 1938 and in the same year was found to have active pulmonary tuberculosis. It seems most likely that this man either had tuberculosis when he left the township before the 1937 survey or else developed it while in Oregon. The second case is that of a man who was first examined in 1934 after years of household contact with a positive-sputum case. At this time his X-ray film showed a discrete, apparently fibroid infiltration in the left upper lobe which was not typical of tuberculosis and a bilateral, basal lesion suggesting bronchiectasis. The patient had no symptoms at this time and sputum examinations were not made. In 1939 there was an increase in the lesion in the left base. There were still no pulmonary symptoms. Sputum examinations were advised but specimens were never submitted. In 1943 he was admitted to the sanatorium with symptoms of one year's duration and with obvious, extensive tuberculosis with cavitation throughout the upper half of the left lung. It seems most probable that the pulmonary lesions seen in 1934 were actually tuberculous, although they were not recognized as such. However, because of the possibility that these 2 men may have developed tuberculosis in the township after the 1937 survey they are both so tabulated.

The total population of the township in 1937 and the age and sex distribution are known from the census taken during our 1937 survey. From the federal census of 1930 we know that the population at that time was 365 as compared to 367 in 1937. We also know that the population of the community was very stable in the intervening years. It therefore seems reasonable to consider a popu-

lation of 366 with essentially the same age and sex distribution as in our 1937 survey as average for the community from 1930 through 1936.

By 1940, according to the federal census, the population had fallen to 337 and in 1944 the census, taken as a part of our survey, showed only 294 people, with an age and sex distribution considerably different from that of 1937. From everything we know of the community we feel that the decrease in population in all probability did not begin until 1939 and that for 1938 the total population as well as the age and sex distribution of 1937 are applicable. For the years 1939 to 1943 inclusive we have estimated the number of persons in each age-sex group, assuming that, in each group where there has been a substantial decrease, the decrease followed that of the total population. In the one group where an increase occurred (males, age 0 to 14) and in the three groups where the decrease was very small (females, age 25 to 44; males, age unknown; females, age un-

TABLE 1  
*Population and new cases of tuberculosis by age and sex*

AGE	POPULATION 1937		POPULATION 1944		ESTIMATED AVERAGE POPULATION 1938-1944 INCLUSIVE		NEW CASES OF TUBERCULOSIS 1930-1936 INCLUSIVE		EXPECTED NEW CASES OF TUBERCULOSIS 1938-1944 INCLUSIVE	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
<i>years</i>										
0-14	35	46	45	40	40.6	42.9	0	0	0	0
15-24	42	38	10	20	25.2	28.6	9	2	5.4	1.5
25-44	56	37	34	36	44.5	36.4	5	2	4.0	2.0
45 and over	66	44	55	38	60.2	40.8	1	0	.9	0
Unrecorded	2	1	8	8	5.0	4.6	0	0	0	0
Totals.....	201	166	152	142	175.5	153.3	15	4	10.3	3.5
Combined totals for both sexes.....	367		294		328.8		19		13.8	

known) we have spread the change evenly throughout the seven years under consideration. To obtain an average population for the years 1938 to 1944 inclusive, we have averaged the estimated numbers in each age-sex group for the years 1938 through 1943 and the known numbers in each similar group in 1944. For each age-sex group in this average population we have then estimated the expected incidence of new cases of tuberculosis from the known incidence by age and sex in the years 1930 through 1936. By this method we have calculated that, if the tuberculosis experience of the community had remained unchanged, a drop in the incidence of new cases from 19 in the seven years before the survey to 13.8 in the seven following years would be anticipated because of the change in the composition of the population (table 1).

The tuberculosis experience of the whole county improved somewhat in the period under consideration and the township we are studying may have shared

in this improvement. Since reliable morbidity rates for the whole county are not available, we have averaged the tuberculosis mortality per 100,000 population (white residents dying in the county) for the years 1930 to 1936 inclusive, and for the years 1938 to 1944 inclusive. The respective average rates are 43.5 and 31.2. We have corrected the expected incidence of 13.8 by the ratio  $\frac{31.2}{43.5}$  and have calculated that, considering both the change in the population and the improvement in tuberculosis experience in the county, 9.9 new cases of tuberculosis would have been expected to develop in this township in the years 1938 through 1944 if no survey had been made.

If the difference between an expected incidence of 9.9 new cases and an actual incidence of 2 new cases is tested by the Chi square method, we obtain a Chi square value of 6.2 and a P of slightly over .015. In other words, there is slightly less than one chance in 66 that the difference between the expected incidence and actual incidence could be due to chance.

There are five obvious probable errors in this study. These errors are additive and all act to diminish the apparent significance of the 1937 survey. First, the 2 persons listed as new cases of tuberculosis developed in the township after the 1937 survey, in all probability developed their disease before the survey was made or, in the case of one of them, in another part of the country. Second, the cases of tuberculosis in which the date of onset could not be determined were not tabulated. There were 15 such cases. All of them developed their tuberculosis before the 1937 survey was made and it seems likely that some of them developed their disease in the years 1930 through 1936. Third, because of the way in which the cases tabulated as occurring in the period 1930 through 1936 were found, it is quite likely that a few cases in this period could have been missed. After the survey in 1937, we were very interested in the possibility of new cases developing in the community and it seems very unlikely that even one case was missed in this period. Fourth, cases of tuberculosis developing during the year 1937 were not tabulated. We felt that the survey made 1937 an abnormal year for statistical consideration in that possibly some cases discovered during the survey would otherwise not have been diagnosed, and that to include them might unduly weight the tabulation of cases occurring before the survey was made. Actually there were 3 such cases with their onset in 1937 and all occurred before the survey was made. Fifth, the correction made for the improvement in the tuberculosis experience of the whole county for the periods under consideration may involve a double correction for the change in population in this township, since it seems likely that a part of the improvement in mortality in the county as a whole may have been due to a change in the population of the county similar to the change which occurred in the township and for which a separate correction was made. This seems most likely since the population of the whole county decreased by 12 per cent from 1940 to November, 1943, as compared to a decrease of 13 per cent in the township from 1940 to 1944. A consideration of these sources of error makes it appear likely that there is really considerably less than one chance in 66 that the difference between the observed and estimated number of new cases of tuberculosis is due to chance.

We find, therefore, that a complete community survey for tuberculosis with hospitalization and treatment of all active cases and follow-up of all inactive cases was followed by a sharp drop in the incidence of new cases of tuberculosis. At least 19 new cases had appeared in the seven-year period preceding the survey. Considering the factors, with the exception of the survey, which might have been expected to result in improvement, 9.9 cases would have been anticipated in the succeeding seven-year period. Actually, only 2 were found and it is likely that both of these developed before the survey was made. Since statistical analysis makes it appear unlikely that such an improvement could have occurred by chance, we conclude that it was probably the result of the complete community survey and hospitalization of active cases.

The assumption that a similar survey would be equally effective in any community would appear unwarranted by the present evidence. First, a fairly stable population would appear necessary if such a good result from a single community examination is to be expected. Second, it is by no means certain that in a community with much less tuberculosis the results would be equally satisfactory, since in such an area, with less chance for exogenous infection, a higher proportion of new cases may occur as the result of endogenous reinfection. Third, although it seems very probable that the community survey was actually responsible for the greater part of the improvement observed in this community the possibility that chance alone may have produced an equal improvement must still be considered, although it is somewhat less than one chance in 66.

#### CONCLUSIONS

1. A complete community survey for tuberculosis conducted in 1937, with hospitalization and treatment of all active cases and follow-up of all inactive cases, was followed immediately by a sharp drop in the incidence of new cases of tuberculosis that has continued to date.
2. A statistical analysis supports the assumption that the community survey was responsible for at least a large part of the improvement observed.
3. The sharp drop in morbidity following the survey would suggest that in this community the majority of cases of clinical tuberculosis have been the direct result of exogenous infection.
4. It would be desirable to use complete community surveys for tuberculosis in other communities of larger size and of various types, and especially in communities with a lower incidence of tuberculosis, so that the value and limitations of the method can be discovered.

#### CONCLUSIONES

1. Una completa encuesta colectiva de la tuberculosis, llevada a cabo en 1937, y seguida de la hospitalización y el tratamiento de todos los casos activos y la observación de todos los inactivos, fué seguida inmediatamente de una baja decidida en la incidencia de casos nuevos, que ha continuado hasta la fecha.
2. Un análisis estadístico apoya la suposición de que a la encuesta se debió por lo menos en gran parte el mejoramiento observado.

3. La baja aguda de la morbilidad después de la encuesta indica que en la colectividad de que se trata, la mayoría de los casos de tuberculosis clínica han sido resultado directo de infección exógena.

4. Parece conveniente ejecutar encuestas colectivas completas en cuanto a tuberculosis en otras colectividades mayores y de distintos tipos, y sobre todo en las que muestren coeficientes tuberculosos bajos, a fin de poder determinar el valor y las limitaciones de este método.

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# TUBERCULOSIS IN SANATORIUM PERSONNEL<sup>1</sup>

## A Tuberculin Survey and Incidence of Active Tuberculosis

D. M. LIM-YUEN<sup>2</sup>

### THE PROBLEM

Tuberculosis among nurses has been—and rightly so—a matter of vital concern to hospitals and sanatoria. It has been the subject of considerable investigation, much of which has found its way into the literature. However, little has appeared concerning the problem of tuberculosis infection and breakdown in sanatorium personnel *as a whole*. The present survey is such a study.

This study was concluded during the closing months of the war, at a time when the general manpower and womanpower shortage was seriously affecting staffs of institutions dedicated to the care of the sick. Hardest hit among these were tuberculosis sanatoria where, besides the perennial claim of social isolation of staff, there has been the fear of contagion. While the recent intensified educational campaign among the public concerning tuberculosis and the significance of contact examinations, as well as mass tuberculosis surveys of well people, have aroused intelligent interest in the disease, they have, at the same time, tended in some cases to create an exaggerated fear of the disease. Just how well founded this fear is in actuality merits scientific investigation.

### SURVEY AT MANITOBA SANATORIUM

This survey embraces all 559 members of the staff employed at Manitoba Sanatorium during the six-year period from January 1, 1938 to December 31, 1943. During that period it had been the practice to do routinely a Mantoux test and a roentgenological examination on every employee on his arrival.

The only ones who escaped a Mantoux test have been ex-patients, who are presumed to be positive, and those who previously have had a definite positive reaction recorded. The procedure of the test is that as outlined in the Diagnostic Standards of the National Tuberculosis Association.

If the test does not cause a reaction it is repeated in three months. If a subsequent test becomes positive a chest film is taken at the same time. In any event, a chest film is taken twice a year, and certainly more often if indicated, as by colds, persistent cough, loss of weight, etc.

Of the 559 employed during the six-year period, 450 had left prior to January 1, 1944, and the remainder were on the current staff of that date.

The average age of all staff members on arrival was 25.5 years. The average age of the 232 negative reactors was 23.6 years, of the positive reactors 27.2.

Of the entire staff, 479 were female and 80 male. This included 33 female ex-patients and 26 male ex-patients (table 1).

*Tuberculin Conversion Among Staff:* In this study the term "tuberculin con-

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version" will be used to indicate change from a negative to a positive reaction while in our employ.

Of the 559 employees, 232 had originally negative reactions; 78, or 33.6 per cent of these, underwent tuberculin conversion after a period of exposure, varying from one month to seventy-two months and averaging 8.5 months. In other words, adding the 78 conversions raises the figure for reactors from 58.5 to 72.6 per cent of the overall total for the six years. Obviously no conversion incidence can be deduced from these figures in the absence of the time factor.

To break down the figures in order to show how the nursing group was affected, it was seen that, of the 122 nurses, 93, or 76.2 per cent, were reactors on arrival. Of the 29 negative reactors, 12 became positive, increasing the crude overall percentage for positive reactions from 76.2 to 86 per cent. Of the 61 attendants, 20, or 32.8 per cent, were reactors on arrival. Of the remaining 41 negative reactors, 31 turned positive, giving a final figure of 83.6 per cent for reactors among all the attendants in the six years.

Authors elsewhere have worked out conversion figures. One found some 25 per cent of tuberculin conversions among student nurses upon completion of

TABLE 1

*Staff at Manitoba Sanatorium, 1938-1948 (inclusive), with tuberculin conversion and morbidity*

	MALE	FEMALE	TOTAL
Staff members.....	80	479	559
Number of ex-patients included.....	26	33	59
Number of negative reactors.....	15	217	232
Number of tuberculin conversions.....	5	73	78
Number of staff developing tuberculosis.	0	12	12
Number of deaths from tuberculosis.....	0	0	0

two months' affiliation with a sanatorium, which raised reactors from 77 to 81 per cent (1). Others found that the total incidence of tuberculosis infection increased from 54 to 58 per cent among student nurses at the end of their three years' training (2). Figures, however, are useless for comparison unless expressed in the form of a case rate per 100 per year, or per 1,000 per year. It is proposed here to use the statistical study method of modified life-tables as employed by Frost (3), who used them in computing the risk of persons in familial contact with pulmonary tuberculosis. Puffer, Stewart and Gass (4) employed this method in analyzing the subsequent course of diagnosed cases of tuberculosis. Hilleboe (5) suggested using these tables in estimating survival rates. Barnwell and Beckerman (6) used these formulae to show that there was no influence on the morbidity rate among 611 student nurses due to the specific exposure of one month's training in a tuberculosis service.

The method as it applies in this paper makes use of two formulae as follows:

$$(1) L_x = l_x + \frac{1}{2}(n_x - w_x)$$

$$(2) m_x = \frac{100d_x}{L_x}$$

Because of the shifting population of a staff, computation is based on the mean number present ( $L_x$ ) during the year ( $x$ ). To the number ( $l_x$ ) present at the beginning of the year, will be added a certain number ( $n_x$ ) who entered the experience during the year. Likewise some ( $w_x$ ) will be withdrawn during the year due to illness or removal to some other employment. This number includes those ( $d_x$ ) who developed clinical tuberculosis. Each of the persons thus added to, or withdrawn from, the experience is counted on as having been exposed for one-half year. The attack rate ( $m_x$ ) per 100 per year is arrived at by the second formula.

It is clear that these formulae can be used to estimate morbidity or mortality incidence as well as incidence of tuberculin conversion. In table 2 these formulae are so used, where the conversion rate ( $m'_x$ ) is found by computing  $\frac{100d'_x}{L_x}$  where  $d'_x$  is the number converting during the year.

TABLE 2

*Conversion and morbidity incidences of 232 negative tuberculin reactors, Manitoba Sanatorium, 1938-1943 (inclusive)*

YEAR $x$	NUMBER PRESENT AT BEGINNING OF YEAR $l_x$	NUMBER ADDED DURING YEAR $n_x$	NUMBER WITHDRAWN DURING YEAR $w_x$	MEAN NUMBER PRESENT DURING YEAR $L_x$	NUMBER CONVERTING DURING YEAR $d'_x$	CONVERSION RATE PER CENT PER ANNUM $m'_x$	NUMBER DEVELOPING TUBERCULO- SIS DURING YEAR $d_x$	ATTACK RATE PER CENT PER ANNUM $m_x$
1938	17	19	14	19.5	9	46.1	2	10.2
1939	22	20	13	25.5	4	15.6	2	7.8
1940	29	27	18	33.5	9	26.8	1	2.9
1941	38	35	31	40.0	20	50.0	1	2.5
1942	42	38	40	41.0	13	31.7	1	2.4
1943	40	59	41	49.0	23	46.9	1	2.1
Total.....				208.5	78	37.4	8	3.8

The conversion rate for the six years was 37.4 per cent per annum.

It might be pointed out that incidence figures presented in this paper will tend to be high, as the staff due to wartime conditions turned over rapidly. Since a good proportion of staff stayed only one to four months, they were added and withdrawn in the same year without figuring in the computation of the mean member present; and in tuberculosis, that short period of exposure can be significant.

In order to determine the relationship between the *degree of exposure* to infection and the *incidence* of tuberculosis infection, the whole staff was divided into four groups:

The group of maximum exposure, group A, included nurses, ward attendants or nurses' assistants, cleaners and physicians. The next group, that of moderate exposure, group B, included maids in diet kitchens on the wards, orderlies, laboratory technicians, dieticians, etc. Under group C—a group presumably with minimal exposure as far as work environment was concerned—were placed X-ray technicians, laundry staff, dining-room waitresses, cooks and girls who worked in the main kitchens. It was decided to include a fourth group, who

were theoretically not exposed to any infection from the patient body, that is, office staff, men working in the powerhouse, laborers, etc.

The 78 tuberculin conversions were categorized into these four groups with rather interesting, though not unexpected, results (table 3). It would be safe to assume that the tuberculin conversion rate, or rather the incidence of tuberculosis infection, would be in direct proportion to the amount of exposure to the disease.

While some authors, like Brahdry (7), cannot find themselves in agreement with these findings, there are others who do (8,9,10). Boynton (8) found the tuberculous infection rate in a group of student nurses in a general hospital 100 times greater than in students in the College of Education at the University of Minnesota, and the rate in student nurses on a special tuberculosis service 500 times greater than in the College of Education students.

Notwithstanding the fact that reactors have been known to turn negative (2,8,9,10), it is interesting to note that 19 of our staff with known negative reactions on arrival, after one year or more of service here, still had negative reactions as well as normal chest films. These included a laborer, aged 60

TABLE 3  
*Tuberculin conversion in different exposure groups*

EXPOSURE GROUP	NUMBER	PERCENTAGE
A (maximal)	49	62.8
B (moderate)	28	35.9
C (minimal)	1	1.3
D (nil)	0	0.0
Total.....	78	100.0

(negative after twenty-seven years), a seamstress (twenty years), a stenographer (nine years), 3 waitresses (after seven, four and two years, respectively), 2 laundresses (after six and four years, respectively), a dietician (three years), 8 maids (5 after two years, 3 after one year), and 2 cleaners (one year). If these were categorized into the exposure groups as in table 3, we would have 2 in group A, 9 in group B, 5 in group C and 3 in group D.

*Development of tuberculosis among staff:* It was found that 12 members of the staff developed tuberculosis during their stay. Table 4 gives a summary of these cases (nos. 1 to 12) plus cases 13, 14 and 15.

Cases 13 and 14 developed disease seven and twelve months, respectively, after tuberculin conversion, and seven and six months, respectively, after leaving our employ. Since they were healthy at the time they left the staff they are not included in the computation of morbidity rates. However, it is possible that their disease is traceable to their late work environment. Case 13 is the only nurse in the series of breakdowns.

Case 15 developed disease two years after leaving the staff, during which interval she worked as usher in a theater. She, of course, is omitted from the calculations.

All 12 patients were single females; their ages upon arrival varied from 17 to 36, averaging 23.9 years. Four came from their home, one had just graduated from high school, 6 had been working as domestics elsewhere and one was a stenographer.

It is noteworthy that all 12 were employed here in positions that come under the maximal and moderate exposure groups, A and B. Eight of the 12 were attendants (A), 2 were cleaners (A) and the remaining 2 were diet kitchen maids

TABLE 4

*Summary of cases developing disease during staff tenure at  
Manitoba Sanatorium (1938—1943, inclusive)*

CASE NUMBER	SEX	AGE	MONTHS ON STAFF	EMPLOYED AS	EXPOSURE GROUP	TUBERCULIN TEST AT ENTRY	MONTHS UNTIL FIRST RECORDED POSITIVE TUBERCULIN TEST	ENTRY CHEST FILM	FILM AT TUBERCULIN CONVERSION	MONTHS AFTER CONVERSION UNTIL FIRST EVIDENCE OF CLINICAL TUBERCULOSIS	TYPE OF DISEASE	DISPOSAL	PROGRESS
1	F	28	6	Cleaner	A	+		Neg.			Pul./Min.	San.	Recovered
2	F	25	10	Attendant	A	+		Neg.			Pleurisy with effusion	San.	Recovered
3	F	21	56	Ward maid	B			Neg.			Pul./Min.	San.	Recovered
4	F	17	102	Attendant	A			Neg.			Pul./Min.	San.	Recovered
5	F	18	19	Cleaner	A	0	4	Neg.	None	8	Pul./Min.	San.	Recovered
6	F	36	5	Attendant	A	0	5	Neg.	TB	0	Erythema nodosum	San.	Recovered
7	F	23	3	Attendant	A	0	3	Neg.	TB	0	Pul./Min.	San.	Recovered
8	F	24	4	Attendant	A	0	3	Neg.	TB	0	Tr.—Br. Adenitis	Home	Recovered
9	F	25	5	Attendant	A	0	5	Neg.	TB	0	Tr.—Br. Adenitis	San.	Recovered
10	F	24	3	Attendant	A	0	3	Neg.	TB	0	Pul./Min.	San.	Recovered
11	F	22	9	Ward maid	B	0	5	Neg.	TB	0	Pul./Min.	San.	Recovered
12	F	24	21	Attendant	A	0	5	Neg.	Neg.	17	Pleurisy with Effusion	San.	Recovered
13	F	23	3	Nurse	A	0	3	Neg.	Neg.	7	Pul./Min.	San.	Recovered
14	F	23	7	Attendant	A	0	3	Neg.	Neg.	12	Pleurisy with Effusion	Home	Recovered
15	F	20	7	Ward maid	B	0	19 (P)	Neg.	TB	0	Pul./Min.	San.	Recovered

on the wards (B). Thus there were 10, or 83.3 per cent of those who developed active tuberculosis, belonging to group A, and 2, or 16.7 per cent, to group B.

Ten of the 12 cases had tuberculin tests on arrival. Cases 3 and 4 came in 1934 and 1930, respectively—before routine entry tuberculin tests were being done here. They were found subsequently to be positive. Cases 1 and 2 had positive tuberculin tests on arrival. The remaining 8, or 66.6 per cent of the total, had negative tuberculin tests which changed to positive in three to five months.

In 7 of the 10 conversions in our series, films were taken when the tuberculin tests were found to be positive. In 6 of the 7, the films showed evidence of

disease. The known time which elapsed between tuberculin conversion and the finding of tuberculosis in the remaining case (case 12) was seventeen months. In the one case (case 5) in which no film was taken at the time of conversion, the disease process was not discovered until eight months later. Seven months after disease was recognized, it had progressed from minimal to moderately advanced—one of only 2 cases in this series in which progression occurred.

TABLE 5  
*Type of disease in the 12 cases with active tuberculosis*

TYPE OF DISEASE	NUMBER	PERCENTAGE
Minimal pulmonary.....	7	58.3
Pleurisy with effusion.....	2	16.6
Tracheobronchial adenitis.....	2	16.6
Erythema nodosum.....	1	8.5
Total.....	12	100.0

TABLE 6  
*Morbidity incidence among 559 staff members, Manitoba Sanatorium, 1938-1943 (incl.)*

YEAR	NUMBER PRESENT AT BEGINNING OF YEAR $l_x$		NUMBER ADDED DURING YEAR $n_x$		NUMBER WITHDRAWN DURING YEAR $w_x$		MEAN NUMBER PRESENT DURING YEAR $L_x$			NUMBER DEVELOPING ACTIVE TUBERCULOSIS DURING YEAR $d_x$		ATTACK RATE PER 100 PER ANNUM $r_x$		
	A	B	A	B	A	B	A	B	AB	A	B	A	B	AB
1938	29	102	5	41	5	32	29	106.5	135.5	0	3	0	2.8	2.2
1939	28	111	1	36	1	40	28	109.0	137	0	5	0	4.6	3.6
1940	28	107	5	46	3	35	29	112.5	141.5	0	1	0	0.8	0.7
1941	30	118	3	58	4	71	29.5	111.5	141	0	1	0	0.9	0.7
1942	29	105	8	70	7	71	29.5	104.5	134	0	1	0	0.9	0.7
1943	30	104	7	94	9	76	29	113.0	142	0	1	0	0.8	0.7
Total.....							174	657	831	0	12	0	1.8	1.4

A—with previous tuberculosis.

B—without previous tuberculosis.

The other case was case 6 in which tracheobronchial adenitis was diagnosed in addition one month later.

In all, the extent of disease was slight, as may be seen from tables 4 and 5. With the exception of one who elected to take treatment at home, all were treated at the Sanatorium. Of special significance in appraising the problem of tuberculosis developing in hospital and sanatorium personnel is the fact that all 12 recovered.

With 12 persons developing tuberculosis out of a staff of 559, the cumulative incidence over the six years is 2.1 per cent. Using the modified life-tables again,

we find the actual morbidity incidence to be 1.4 per cent per year (table 6). The rate of new cases can be calculated by removing from the experience those who had previous tuberculosis; the resulting incidence is then 1.8 per cent per year.

Since 8 of the 12 were from originally negative reactors, the morbidity incidence in that negative tuberculin group is 3.8 per cent per year (table 2).

If we presume cases 3 and 4 (table 4) to have been originally positive, the morbidity incidence in the positive tuberculin group, calculated by combining table 2 and table 6, is 0.89 per cent per year, at least one-fourth the incidence in the negative reactor group.

As was pointed out before, little appears in the literature concerning the incidence in the personnel of a sanatorium as a whole, but much is reported regarding morbidity in nurses-in-training in general hospitals. However, in many cases either no true incidence figures are given, or else they are arrived at by other methods than those employed here, so that they are not suitable for comparison.

Ross (11) described in 1930 a series of 60 nurses with tuberculosis in Manitoba, 50 of whom broke down during their training or within one year of graduation, giving a cumulative figure of 6 per cent of the nurses in training in Manitoba during that same four-year period.

Amberson and Riggins (12) revealed a morbidity rate of 1.09 per 100 nurses per year in a five-year study of tuberculosis among 492 students in Bellevue Hospital, School of Nursing, New York City.

Jones (13) in 1933 reported a morbidity rate of 3 per cent per annum among 169 nurses and associates in a New Zealand Hospital.

Scott (14) in an unpublished survey described a total of 29 nurses who developed tuberculosis in the ten-year period of 1934-1943 (inclusive) during which 744 girls were admitted for training in the Winnipeg General Hospital, Winnipeg, Manitoba.

Recently there have been two comparable studies using the modified life-table formula. Beckerman (15) found the incidence of tuberculosis in a group of nursing students to be 1.22 per 100 per year. Muschenheim, Bunn and Lansdown (16) have published their observations among 773 medical students, 509 nurses and 2,166 graduate nurses, and found the rate to be 0.2, 0.52 and 0.6 per cent per year, respectively.

It might be fitting here to cite some figures from industrial surveys. Fellows (17) gives the case rate of tuberculosis among 4,000 female employees of the Metropolitan Life Insurance Company (1932-1935) as 0.25 per cent per year. Reid (18), in a study of clerical employees over a ten-year period (1930-1939) gives her figures as 0.21 per 100 males per year and 0.25 per 100 females per year. Although the age groups studied are comparable with the nursing groups, there are some differences, such as in degree of exposure to disease, population turnover, methods of calculation and diagnostic procedures (fluoroscapy was used to a great extent rather than roentgenography).

## DISCUSSION

It has been shown that 98.7 per cent of the tuberculin conversion (table 2) and 100 per cent of the staff members who developed active tuberculosis (table 4) came from groups subjected to maximal and moderate exposure to disease.

Nurses and attendants are exposed to the same hazards. With the exception of the one questionable case (case 13), not a single nurse out of 122 (with 2,811 total observation months) developed disease. Yet 8 attendants out of 61 (with a total observation period of 1912 months) contracted tuberculosis; these 8 constituted two-thirds of all who developed active tuberculosis. The number of persons involved is too small to draw any definite conclusions, but the difference in morbidity figures between these two groups is impressive and raises serious medical and administrative problems.

It is true that the nurses are of a slightly older age group than the attendants. It has been shown that 76.2 per cent of the nurses were reactors on arrival, while the figure for attendants was 32.8 per cent. But we feel that the largest factor in ensuring the safety of nurses from disease is the discipline and training of their profession. Offsetting her increased exposure to disease in the sanatorium are the facts that her work is lighter than that of the nurse in a general hospital, her hours more regular, her training in the care of infectious diseases more specialized. The diagnosis of tuberculosis is presumed from the moment of admission of all patients, and adequate protection is used. The nurse in a general hospital, on the other hand, may be caring for a medical or surgical patient for some time before it is discovered that he has open tuberculosis as a concomitant disease.

The young women who apply for a position as attendant, cleaner or ward maid usually come from the surrounding rural areas where they have had little or no exposure to tuberculosis. They are of varying intellect and intelligence, and they are usually young; this was especially true during the war. Their knowledge of disease and asepsis has often been elementary indeed. It is in this group, predominantly tuberculin-negative as it turned out to be, that morbidity has been so high. Therefore, the problem becomes one of education as soon as they are employed in the sanatorium. The time factor is of vital importance. Thorough and repeated instructions have to be given on wards and in lecture rooms. Detailed isolation technique must be taught and rules rigidly enforced, details that include the use of gown, the keeping of contaminated fingers from face and hair, the proper disposal of sputa and excreta. Other factors are more personal but equally significant. What the employees of an institution do with their spare time is rightly their own concern unless their activities lower their resistance and render them more susceptible to infection. It must be emphasized that exercise and fresh air are essential, but adequate rest and sleep are paramount, in other words, that their energy expenditure is a budgetable item. They need to be reminded, while on the wards, that, though their duty lies in contributing to the patient's recovery, any association with him beyond the performance of this duty is courting trouble. It is not difficult

in the informal atmosphere of a sanatorium to drift from the one extreme of fear of the disease to the other extreme of contempt of it.

The patient, of course, must be taught to coöperate intelligently and learn a technique for the protection of others from his disease. Without this coöperation the whole scheme of prophylaxis becomes futile.

Rigid enforcement of these protective measures may accomplish much, but in spite of all precautions it seems inevitable that some will acquire the infection. It has been pointed out that in the present series the percentage of disease among the negative reactors is at least four times greater than among the positive reactors. Of those who developed active tuberculous 8, or 66.6 per cent, were originally negative reactors. Amberson and Riggins (19) stated that 75 per cent of their student nurses who developed active disease were originally negative reactors. It can be no mere coincidence that others (7, 9, 10, 21) have found similar results. It would seem, then, not illogical to presume that a tuberculin allergy confers some measure of immunity on its possessors. Numerous attempts have been made in the past to find some means to immunize against tuberculosis, but to date they have ended in failure, with the one possible exception of BCG vaccination of negative reactors. The swing in favor of BCG inoculation in various places, in Canada notably in Quebec under Frappier (20) and in Saskatchewan under Ferguson (21), has been gaining considerable momentum.

In conclusion it might be pointed out that in each of the 12 cases of tuberculosis the amount of disease was slight, the symptoms when present were light, the infectivity small or nil, the mortality zero. All 12 patients recovered within a relatively short time, and are now leading practically normal lives. This undoubtedly redounds to the early and persistent case-finding methods employed here, embracing the use of routine tuberculin tests, frequent X-ray examinations, close supervision and physical examinations when deemed necessary.

It is fair to speculate that, had such methods of supervision not been employed, a smaller number with disease would have been discovered. The outcome might conceivably be that some of the undiscovered cases would have recovered without treatment, while a small percentage might have progressed to advanced disease before detection.

#### SUMMARY

1. A survey is presented of tuberculin sensitivity and incidence of tuberculin conversion and development of active tuberculosis in 559 staff members employed at Manitoba Sanatorium during 1938-1943, inclusive.

2. Conversion and morbidity rates are computed from modified life-tables, suggested by Frost.

3. Of the 232 negative reactors, 78, or 33.6 per cent, became positive, the tuberculin conversion rate being 37.4 per cent per annum.

4. Staff members exposed most heavily to disease constituted 98.7 per cent of the conversions.

5. There were 12 cases of active tuberculosis, representing a morbidity in-



cidence of 1.4 per cent per annum, or an attack rate of new cases of 1.8 per cent per annum. There were 7 cases of minimal pulmonary disease, 2 of pleurisy with effusion, 2 of tracheobronchial adenitis and one of erythema nodosum. They were all from two groups with definite exposure. They all recovered.

6. Morbidity incidence among the originally negative reactors was 3.8 per cent per annum, that among the positive reactors was 0.89 per cent per annum.

7. No nurse developed tuberculosis, while 8 attendants did.

8. The question is brought up of better educational and preventive measures in safeguarding the staff, and a plea is made that provision for some specific protection be considered, such as BCG vaccination.

#### SUMARIO

1. Preséntase un estudio de la sensibilidad a la tuberculina y la incidencia de conversión (viraje) a la tuberculina y aparición de tuberculosis activa en 559 empleados del Sanatorio de Manitoba en 1938-1943, inclusive.

2. Los coeficientes de conversión y morbilidad fueron computados conforme a las tablas de vida modificadas, que propusiera Frost.

3. De los 232 negativos, 78 (33.6 por ciento) se volvieron positivos, siendo el coeficiente anual de conversión a la tuberculina, de 37.4 por ciento.

4. Los empleados más intensamente expuestos a la enfermedad constituyeron 98.7 por ciento de las conversiones.

5. Hubo 12 casos de tuberculosis activa, representando una morbilidad de 1.4 por ciento al año, o un coeficiente anual de ataque de 1.8 por ciento en casos nuevos. Hubo 7 casos de afección pulmonar mínima, 2 de pleuresía con derrame, 2 de adenitis traqueobronquial y uno de eritema nudoso, procediendo todos ellos de dos grupos en que había exposición bien definida. Todos se repusieron.

6. La morbilidad entre los primitivamente negativos representó 3.8 por ciento al año; entre los positivos 0.89 por ciento.

7. Ninguna enfermera manifestó tuberculosis; 8 asistentes sí la manifestaron.

8. Suscítase el punto de perfeccionar las medidas educativas y profilácticas para proteger a los empleados, y abógase por la consideración de alguna disposición específica, por ej., vacunación con BCG.

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# A TUBERCULOSIS SURVEY IN A PRIVATE HOSPITAL<sup>1</sup>

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In recent years, there have been several important contributions to the subject of unrecognized pulmonary tuberculosis in general hospitals.

In 1932, Mills and Stewart (1) examined 353 patients admitted to the Swedish Hospital in Minneapolis and found that 1.4 per cent of the total had reinfection type tuberculosis.

In 1935, Hodges (2) of the University of Michigan conducted a chest X-ray survey of 1,101 patients admitted consecutively either to the University Hospital or its out-patient clinic during a period of fourteen days and in 1.3 per cent found "significant chest disease unrecognizable by other methods and often totally unexpected on the basis of chief complaint and history."

In 1935, Pohle, Paul and Oatway (3) of the Wisconsin General Hospital took chest X-ray films of 1,417 patients admitted during a three-month period. About 3 per cent of the total number receiving X-ray examinations of the chest had significant disease which was not detected clinically, and 0.3 per cent were found to have active reinfection type tuberculosis.

Plunkett and Mikol (4) in 1940 conducted chest X-ray examinations of 4,853 patients admitted to general hospitals in upstate New York and found a prevalence of 2.6 per cent with evidence of reinfection type tuberculosis. Of these, 1.1 per cent had roentgenological characteristics of clinically significant lesions.

In 1943, Childress, Debbie and Harmon (5) reported on a tuberculosis case-finding demonstration at Grasslands Hospital, Valhalla, New York. This study extended over a period of eighteen months during which time 7,187 patients were X-rayed. Of these, 2.8 per cent were found to have evidence of reinfection type tuberculosis, and activity was established in 0.35 per cent of the total examined.

In 1944, Bloch and Tucker (6) reported on routine fluoroscopic examinations among the patients of the University of Chicago Clinics. The results obtained from the first 15,000 patients so examined showed that 4.17 per cent of the total number were found to have tuberculous lesions of the reinfection type. In 1.43 per cent, these lesions were recognized as "clinically important."

In this paper we are reporting on a similar tuberculosis case-finding survey, conducted by the Queensboro Tuberculosis and Health Association, at Flushing Hospital, Flushing, New York. The study began on August 1, 1944 and was terminated on July 31, 1945.

## METHOD OF PROCEDURE

Before the study was undertaken, the proposal was submitted to the Board of Directors and the Medical Board of Flushing Hospital for approval. Letters

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<sup>3</sup> In charge of nurses and technicians who coöperated in this study.

were addressed to the attending, nursing and courtesy staffs to inform them of the project and to urge their coöperation.

An X-ray unit was set up on the first floor of the hospital where chest films were taken from 9 a.m. to 5 p.m. except Saturday afternoons and Sundays. Powers' 14 x 17" paper X-ray method was used.

The survey was inaugurated in the out-patient department of the hospital. Patients were X-rayed immediately after registering for clinic. Those patients with positive X-ray findings were referred to the tuberculosis association's Consultation Chest Clinic, held in the hospital twice each month. This recheck included an examination by a chest specialist and a roentgenogram on 14 x 17" celluloid film. Paper X-ray and subsequent celluloid films were read by the association's clinicians. The procedure used in the out-patient clinics provided a smooth and efficient method of conducting such a survey.

The X-raying of in-hospital patients was begun in October, 1944. Letters were sent to private physicians informing them of the survey, asking their permission to X-ray each private patient immediately after leaving the admitting office. Of the 118 physicians on the staff, 80 consented to have their patients X-rayed. Although the coöperative private physicians urged their patients to participate in the survey, chest X-raying was not made compulsory. Many patients were too ill on admission to be X-rayed at that time. In such cases, arrangements were made for a chest X-ray examination of the patient whenever he could be moved. Some patients during the entire period of their hospitalization were too ill to be moved. Others were in casts and could not be X-rayed. Still others were discharged during the evening and over weekends and, therefore, were not included in the survey.

#### RESULTS

A total of 3,487 persons were included in the study. Of these, 1,653 were out-patients, representing 97 per cent of the total registered during the period. Of the in-patients admitted during this period, 1,834, or 44 per cent of the total, were X-rayed. (Of this group 83 per cent were private patients.)

Of the 3,487 patients X-rayed, 112, or 3.2 per cent, showed evidence of reinfection type tuberculosis. Of these, 21, or 0.6 per cent of the total X-rayed, showed evidence of active tuberculous disease. (Three additional cases showed changes suggesting active disease on the paper roentgenogram, but could not be definitely diagnosed because follow-up was not possible.) The hospital records of 8 of the 21 active cases showed that the disease was suspected by the attending staff. In the remaining 13 cases, or 0.37 per cent of the total group studied, tuberculosis had not been considered, and the survey X-ray film revealed the first evidence of the disease. Of the 13 active cases, 7 were in the minimal stage and 6 were moderately advanced.

In addition to the cases of tuberculosis discovered in this study, 126, or 3.6 per cent of the total X-rayed, were found to have cardiac abnormalities. The X-ray films of 72, or 2 per cent, showed evidence of various significant pulmonary conditions such as pneumonia, pleural effusion, carcinoma, etc. Approximately

40 per cent of these cardiac and other thoracic conditions were unsuspected before the X-ray films were taken.

#### SUMMARY

From August, 1944 to July, 1945 the Queensboro Tuberculosis and Health Association conducted a tuberculosis case-finding program at the Flushing Hospital, New York.

A total of 3,487 patients was X-rayed. Of these, 112, or 3.2 per cent, were found to have reinfection type tuberculosis; 21, or 0.6 per cent of the total X-rayed, showed evidence of active tuberculous disease. In 13 of the patients found to be active, or 0.37 per cent of the total X-rayed, the disease was not suspected before X-raying.

#### SUMARIO

De agosto, 1944, a julio, 1945, la Asociación contra la Tuberculosis y Pro Salud de Queensboro llevó a cabo una obra de descubrimiento de casos de tuberculosis en el Hospital de Flushing, Nueva York.

Se radiografió en conjunto a 3,487 personas, de las cuales, 112 (3.2 por ciento) mostraron tuberculosis tipo reinfección y 21 (0.6 por ciento), signos de enfermedad tuberculosa activa. En 13 de los casos activos (0.37 por ciento del total radiografiado), no se sospechaba la presencia de la enfermedad antes de tomar la radiografía.

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# PREGNANCY AND TUBERCULOSIS<sup>1</sup>

## The Present Status of the Problem

LOUIS L. FRIEDMAN<sup>2</sup> AND JAMES R. GARBER<sup>3</sup>

Phthysiologists and obstetricians have long recognized the cause and effect relationship of pregnancy to pulmonary tuberculosis as one of the most perplexing and controversial problems of medicine. Therefore, this study of the available pertinent literature on the subject has been undertaken in an attempt to ascertain the exact status of the problem to-day and to delineate existing clinical opinions and impressions.

Tuberculosis ranked first as a cause of death at the turn of the century, but to-day it has been relegated to seventh place for the overall population. Death rates for tuberculosis have been much reduced in women of all ages, but in females of the child-bearing years one out of six deaths is due to tuberculosis and as such it is still the leading cause of death in this group of women, ages 15 to 44 (30, 45). Although about 32,000 pregnancies occur in tuberculous females annually (33), this fact, in itself, is not sufficient evidence to justify the contention that pregnancy predisposes to tuberculosis (46) and is therefore accountable for our failure to control the disease in this age group. The high incidence of both these conditions in females of the child-bearing years is a more likely interpretation of their frequent coexistence (30, 42). As yet, no satisfactory explanation has been offered which accounts for the continued high incidence of tuberculosis in young females. When tuberculosis is complicated by the added risks of pregnancy, the physician and the patient face a truly formidable problem. For the most part, the available literature on the subject is confusing and recorded statistics are unreliable because of the paucity of cases correctly studied and the uncorrelated nature of the investigations conducted. The type of management recommended for these cases is usually the consequence of empirical teachings and limited clinical experience and observations. Actually we have not progressed much further than Hippocrates who believed that "pregnancy is the best cure for consumption." (7, 15, 21)

This erroneous clinical impression of one of our foremost ancients was shared by such eminent physicians as Rokitsansky, Warren and Clark; and as late as 1918, by Sabourin (5, 22). It remained unchallenged until the middle of the nineteenth century when Louis cast doubt upon its validity and suggested that pregnancy may actually be harmful when it complicates pulmonary tuberculosis (21). This observation and the teachings of Grisolle helped to liberate the pendulum of medical opinion from the shackles of the age-honored Hippocratic doctrine, but it did not stop until it was anchored to the equally extreme and erro-

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neous dicta of Schauta and Young (15, 34, 40). Schauta advocated therapeutic abortion in all pregnant tuberculous females, and Cohen quotes Young's advice: "If a virgin, no marriage; if married, no pregnancy; if pregnant, no confinement." (7, 34) The Germans oversubscribed to these radical views and in the early part of the twentieth century advocated routine therapeutic abortion when pregnancy occurred in a tuberculous female (15, 41). However, the era of speculation and extremes has gradually succumbed to a more scientific and accurate clinical appraisal of the problem. To-day no well-informed physician believes that pregnancy cures tuberculosis or that pregnancy should never be advised or continued in a pregnant tuberculous female (17).

In the past twenty or thirty years, some limited, but nevertheless real efforts have been made by the obstetrician and phthisiologist to evaluate this problem on a more rational and scientific basis. In 1918, Norris and Landis observed that the onset of tuberculosis in young females was frequently associated with pregnancy or the puerperium (29). This view was shared by many clinicians at that time and is still subscribed to by a few to-day (47). However, in 1938, Jameson published the results of his careful investigation which indicated that there was very little, if any, evidence that tuberculosis was more frequent in the pregnant state or immediately thereafter (21). Recently, fluoroscopic and X-ray examinations of all pregnant females in large prenatal clinics have revealed an incidence of from 0.7 per cent to 1.8 per cent of clinically important tuberculosis (13, 16, 18, 43). These results are not unlike those obtained for non-pregnant females of the same age group. The statistical differences in the reported incidence of the disease in pregnant females undoubtedly reflect the socio-economical status of the group investigated. Then again, the diagnostic criteria of the various investigators may influence the reported incidence of clinically important tuberculosis. In any event, these reported differences are not to be taken too seriously.

Norris and Landis, Young and other authors believe that pregnancy, labor and the puerperium influence the course of the tuberculous process adversely (2, 4, 15, 19, 20, 29, 33, 39, 40, 46, 47). They offer evidence to the effect that the disease is more frequently exacerbated during pregnancy. Cutler has concluded from his careful investigation that pregnancy is contraindicated in active tuberculosis as it influences the course of the disease adversely but does not affect the arrested, well treated and stabilized process (10). However, this view is not shared by such authors as Ornstein and Epstein, Ornstein and Kovnat, Barnes and Barnes, Hull and others. They believe, according to their recent studies, that pregnancy, labor and the puerperium do not influence the course of tuberculosis (3, 8, 17, 21, 25, 30, 31, 34). Instead, they feel that the prognosis is influenced chiefly by the nature of the disease and the institution of early, adequate and proper treatment. Ornstein and Kovnat, and Barnes and Barnes found that the fatal outcomes were almost uniformly confined to the caseous-pneumonic and far advanced cases of tuberculosis (3, 30, 31). Skillen and Bogen, and Burke, working with control groups of pregnant and nonpregnant tuberculous animals, have confirmed the conclusions of these investigators (6, 40). To-day

the prevailing opinion among leading clinicians is in agreement with the general impression that pregnancy exerts little or no effect upon the incidence or course of pulmonary tuberculosis (25). However, there is a small group of conservative investigators who are still unwilling to accept this view without reservation because they feel that in a very small percentage of the cases pregnancy actually exerts a detrimental effect upon the course of pulmonary tuberculosis (3, 10, 26b, 37). They contend that the results achieved with the more heroic and effective measures available for the treatment of pulmonary tuberculosis to-day are responsible for the apparent innocuous relationship between pregnancy and phthisis. This restraining influence is very desirable as it will aid in arriving at a more permanent and satisfactory solution to this controversial problem.

Some observers feel that pregnancy actually improves tuberculosis, but their observations are probably more fanciful than real (5, 20, 40). Any gain in weight and improvement in the general well-being of tuberculous females who become pregnant are only deceiving reflections of the normal course of events in pregnancy (17, 19). The contention that the elevated diaphragm in pregnancy possesses decreased mobility and exerts a beneficial influence has been disproved by Heynemann and more recently by McGinty (2, 5, 27, 28). The latter has proved in a well-conducted study that the mobility of the diaphragm is not restricted by the enlarged uterus. It may rest at a higher level, but the amplitude of its excursions is the same in both the pregnant and nonpregnant state. From the foregoing observations, one may conclude that pregnancy exerts very little, if any, effect on the incidence or course of tuberculosis in pregnant females. More than likely, the effort of child-rearing exerts a greater influence on the prognosis of the disease than does child-bearing.

To evaluate this problem properly, it is also necessary to consider the fetus of tuberculous mothers. It has been shown that a live birth may be expected in 81 per cent of these pregnancies, and that the fetus is usually normal in all respects (3, 34, 37, 41, 44). However, it is necessary to take special precautions at the time of delivery and to separate the mother and child immediately in order to avoid infection. Transplacental infection is known to occur, but it is so uncommon that it should not enter into a serious consideration of the overall problem (11, 39, 41). If the newborn are properly protected against infection by their tuberculous mothers, the incidence of tuberculosis in these children is essentially not different from that observed in the offspring of nontuberculous females. Some authors believe that premature birth is more frequent in tuberculous mothers and especially in those suffering from far advanced disease, but this opinion is not shared by all investigators and is open to question (9, 26a, 29, 37, 44).

After considering the presently available statistical information and reliable clinical observations concerning the tuberculous maternal organism and her fetus, leading obstetricians and phthisiologists have concluded that therapeutic abortion is never indicated after the first trimester of pregnancy (2, 3, 8, 10, 22, 25, 26b, 28, 29, 34, 37, 41). The risk of this procedure is just as great as full-term delivery and no dramatic therapeutic benefits are to be expected (34). On



rare occasions in the presence of rapidly advancing caseous-pneumonic disease, a therapeutic abortion may be considered and undertaken during the first trimester of pregnancy. However, the benefits to be derived from this procedure are unproved and equivocal in spite of the fact that some authors advocate it quite freely in the face of active disease (1, 4, 10, 19, 29, 40, 41, 47). Conservative management is the solution to the obstetrician's problem, but the phthisiologist's responsibilities in pregnant tuberculous females are much greater. To achieve the best therapeutic results in these instances, it is advisable to treat the tuberculosis as if no pregnancy existed (4). When tuberculosis is first recognized after pregnancy has supervened, the patient should be treated no differently than her nonpregnant sister (7, 8, 36). The phthisiologist should treat this patient energetically and without procrastination. If indicated, some form of collapse therapy, preferably pneumothorax, should be instituted as soon as possible, provided an effective and successful collapse may be anticipated before the expected date of confinement (22, 30, 37). When bilateral disease is present, even bilateral pneumothorax therapy may be started. The successful utilization of bilateral pneumothorax therapy has been reported, and the junior author (LLF) has personally witnessed the uneventful delivery of live, normal children by 2 tuberculous females receiving this treatment (2, 15, 37). However, the best results are obtained when tuberculosis is recognized and treated actively before pregnancy occurs and, if possible, before marriage (24, 37). Lyman has shown that the prognosis is much better in tuberculous females who are single when the tuberculosis is recognized and treated; provided they get married after the disease is arrested (24). These patients fare better than those who are married before their disease is recognized and those who are single when they receive treatment and remain so after their disease is arrested (24).

In considering the therapeutic aspects of this problem, the proper approach would appear to be the earliest possible recognition of the disease in all females who are capable of child-bearing. This may best be accomplished by either mass fluoroscopic or other X-ray examination of all females past puberty at regularly scheduled intervals and in all prenatal clinics (5, 13, 14, 18, 35, 41). In the hands of experts, fluoroscopy has been found to be 91 per cent accurate (32). However, with the advent of the cheaper and unusually rapid methods of conducting mass X-ray examinations of the chest, its apparent advantages have been minimized. Ianne and Muir, and Seid recommend screening with a tuberculin test before fluoroscopy or X-ray examination is performed (18, 38). Frequent X-ray examination is especially indicated in all young females who are members of the lower socio-economic classes. Although careful physical examination of the patient who is suspected of having pulmonary tuberculosis is still advised, it must not be relied upon to establish the final diagnosis (14, 35, 45). Sampson and Brown, and Eisele, Tucker, Vines and Batty have found that the majority of the cases will be missed if this method is used without the beneficial assistance of X-ray examination (14, 35). If the diagnosis is made on the basis of clinical grounds only, Vaughan and Douglas have shown that 80 per cent of the cases will be in a far advanced stage when reported (45). Therefore, in

order to diagnose pulmonary tuberculosis in its minimal or early stages, X-ray examination of the chest should be done as routinely as a Wassermann test for syphilis in all prenatal clinics (12). Eisele and Mason, and Eisele, *et al*, have shown that the incidence of clinically important tuberculosis is more frequent than syphilis in the groups they studied (13, 14).

Next to actual prevention of the disease, the early diagnosis of pulmonary tuberculosis is most important because the expected therapeutic results are directly proportional to the nature and extent of the lesions at the time treatment is instituted (18, 21, 35, 36). The type of therapy employed depends upon a careful and critical evaluation of each case on an individual basis. In some instances, bed-rest may be the preferable form of management and, in others, some form of collapse therapy maybe indicated. With few exceptions, in determining what form of therapy to advise, the problem of the pregnant female should be evaluated on the basis of the same principles and policies which influence the ultimate decision in her nonpregnant sister (7, 8, 26b, 36). If it is possible to induce and maintain a satisfactory collapse, pneumothorax therapy is the procedure of choice. Unilateral and bilateral pneumothorax treatment, if started before pregnancy supervenes, may be continued during the entire period of gestation (2, 10, 18, 37). If pregnancy has already occurred before the diagnosis is established, unilateral or bilateral pneumothorax, as previously indicated, may be initiated if the existing conditions warrant this action. Collapse therapy does not influence the pregnancy adversely and may be a life-saving measure on occasion (37). The pregnant mother tolerates artificial pneumothorax therapy exceedingly well, even bilateral. Occasionally during the last months of pregnancy, she may experience slight dyspnea after each refill. If this symptom is disturbing to the patient, the amount of air given at each treatment may be reduced and refills scheduled more frequently (28). No special measures are necessary at the time of delivery unless there is a marked reduction in intrapleural pressure. In this event, a refill may be in order. Thoracoplasty is a major operative procedure which should never be attempted during any stage of pregnancy. It not only carries a high risk for the mother but may jeopardize the safety of the fetus. However, patients who have had successful thoracoplasties in the past may be permitted to become pregnant if the disease is arrested (10, 37).

Unmarried females may be permitted to marry as soon as their tuberculous process is arrested. The benefits to be derived from a happy and financially sound marriage far outweigh the risks involved, if the patient is coöperative and properly instructed in the technique of contraception. However, if the contemplated marriage will require more physical effort than the patient can safely endure, the physician should advise against it. When financially unsound and possibly unhappy marriages are planned, similar advice is indicated. Of the numerous variables which influence the ultimate prognosis in these patients, the phthisiologist's ability as a sociologist should be second only to his medical prowess if successful therapeutic results are to be achieved.

If the current impression regarding the only casual relationship between

child-bearing and tuberculosis is correct, then pregnancy may actually be permitted at any time during the course of the pulmonary disease. However, most authorities on the subject still believe that pregnancy should not be advised until the disease has been arrested for two or three years (1, 7, 20, 26a, 28, 29, 33, 47). Lyman has expressed the opinion that a one-year interval is sufficient (24), and in so doing has reflected the modern trend to regard pregnancy as a coincidental and innocent companion of existing pulmonary tuberculosis. These advised periods of waiting following the arrest of pulmonary tuberculosis provide the physician with an opportunity to observe the stability of the disease and enable the patient to better prepare herself for the increased physical efforts of child-rearing. Two or possibly three live births may be permitted, but as in all chronic medical conditions frequent and numerous pregnancies are contraindicated (36).

In general, the management of pregnancy in females who have pulmonary tuberculosis presents no special problems (28). However, as in all other tuberculous patients, they should be carefully watched for any signs or symptoms of possible reactivation of the disease. Arrangements should be made well in advance of the expected date of delivery for hospitalization of the patient, preferably in a tuberculosis sanatorium which is properly equipped to provide adequate and special care for mother and child (26a, 37, 47). Unfortunately, there is a woeful lack of such institutions throughout the country (26b). Delivery should be from below, but some steps such as episiotomy and/or low forceps should be taken to speed the second stage of labor. Version and breech extraction should be avoided because of the deep anesthesia required (26b). Caesarean section may be utilized, but is by no means the procedure of choice unless some obstetrical indication for operative intervention exists or if sterilization of the patient has been agreed upon in advance. However, Matthews, Johnson, and Lloyd and Richard believe that caesarean section is the method of choice in managing pregnant tuberculous mothers (4, 22, 23, 26b). In their opinion, it is indicated because it eliminates the voluntary efforts of the second stage of labor and maintains relatively constant intrapleural pressures during delivery. Whether or not these precautions are necessary or actually prevent exacerbation of pulmonary tuberculosis is open to question. The type of anesthesia selected for these cases depends upon the type of delivery and individual preference. Ether, ethylene, nitrous oxide, cyclopropane, spinal and local anesthesia all have their advocates (2, 4, 12, 26b, 28, 33, 37, 42). Following delivery, the newborn should not be permitted to come in contact with the mother; and, to prevent tuberculous infection of the child, lactation should not be permitted (7, 28, 41).

From the foregoing discussion of this problem, it is apparent that the major responsibility in pregnancy complicating pulmonary tuberculosis rests with the phthisiologist and not with the obstetrician. However, to assure successful results, it is necessary for the phthisiologist and obstetrician to manage each case in a spirit of unprejudiced and whole-hearted coöperation. Although the last word has not been written on this controversial subject, the more rational approach to the solution of this problem in the past two or three decades is en-

couraging. We are beginning to accumulate accurate statistics on the basis of scientific clinical observations and research. This steady progress parallels the increased interest of the phthisiologist in this problem while the more optimistic outlook for pregnant tuberculous females reflects the increased utilization of collapse therapy, especially artificial pneumothorax. However, at the present time, early diagnosis and adequate effective treatment are the best insurance for the female of the child-bearing years.

#### SUMMARY

1. The historical and controversial aspects of pulmonary tuberculosis complicated by pregnancy have been presented and discussed.
2. Pregnancy probably exerts little or no influence on the incidence or course of pulmonary tuberculosis.
3. Therapeutic abortion should never be performed after the first trimester of pregnancy and very rarely, if at all, during the earlier months of gestation.
4. The value of routine chest X-ray examinations has been emphasized.
5. Early diagnosis and adequate effective therapy improve the prognosis in females of the child-bearing years suffering from pulmonary tuberculosis.

#### SUMARIO

1. Preséntanse y analízanse aquí las fases históricas y debatidas de la tuberculosis pulmonar complicada por el embarazo.
2. El embarazo probablemente ejerce poco o ningún efecto sobre la incidencia o evolución de la tuberculosis pulmonar.
3. Jamás debe ejecutarse el aborto terapéutico a partir del primer trimestre del embarazo, y muy rara vez o nunca, durante los meses anteriores.
4. Recálcase el valor de los exámenes radiográficos sistemáticos del tórax.
5. El diagnóstico temprano y la terapéutica eficaz mejoran el pronóstico en las mujeres en la edad reproductiva que padecen de tuberculosis pulmonar.

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# SPONTANEOUS HEMOPNEUMOTHORAX

## A Case Report

RAY VANDER MEER<sup>1,2</sup>

Since 1900 approximately 60 cases of spontaneous hemopneumothorax have been reported in otherwise apparently well persons. Excellent surveys of the literature have been made by Jones and Gilbert (7), Hopkins (3) and Hartzell (2). No attempt will be made to review the literature. The following case is reported because of the comparative rarity of the disease.

### CASE REPORT

The patient was a 26 year old white male soldier admitted to the hospital on May 31, 1944 with the main complaint of severe pain in the the left chest and marked dyspnea and cyanosis.

The patient had been entirely well up to 5:30 a.m. on the day of entry when, while filling in a slit trench, he suddenly noticed a sharp pain between the shoulder blades, chiefly on the left side of the spine. He had not previously fallen or received any type of trauma. In the course of the next twenty minutes the patient became extremely dyspneic and cyanotic. He was rushed to the hospital with the diagnosis of "shock."

His past history revealed no similar episode at any time nor had there been any serious illness. In childhood he had measles, mumps and chicken pox and about three years before he had an attack of "flu" which lasted for two weeks and from which he recovered without residual effects. There was no history of surgery except for tonsillectomy and adenoidectomy at the age of seven. Family history was negative for tuberculosis. The patient was married and had no children. Systemic inquiry revealed no history of hemoptysis, cough or loss of weight.

*Physical examination:* The patient appeared acutely ill, markedly cyanotic and dyspneic. The oral temperature was 100°F., pulse 88, respirations 38, blood pressure 82 over 52. Chest examination revealed suppressed breath sounds, decreased fremitus and dullness to percussion over the entire left thorax. The right lung was clear. Heart sounds were faint and distant but were heard best along the right sternal border in the fifth interspace. The rest of the examination was essentially negative.

*Clinical course:* The patient responded well to initial shock therapy consisting of oxygen, intravenous fluids and morphine. He continued to show some respiratory embarrassment for about four days and oxygen was used during this time. For the first three days the patient showed some temperature elevation up to 100°F. Sulfadiazine was given during the first two days and then discontinued. At a diagnostic thoracentesis, done on the ninth day, 60 cc. of pure blood were withdrawn. It was observed that this blood, at the end of sixty minutes, had failed to clot. All blood appeared to have been absorbed from the left thorax by the twenty-fifth day, as determined by physical and X-ray examination. His convalescence continued to be uneventful and the patient was discharged from the hospital on the seventy-second day.

*Laboratory findings:* Blood counts on the second day showed a red cell count of 2,920,000 per cubic mm. and a white cell count of 9,400. Hemoglobin was 9.14 g. The differential

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count showed neutrophils 65 per cent, lymphocytes 31 per cent, monocytes 3 per cent, eosinophils 1 per cent. On the fifth day the blood count showed red cells, 3,630,000; total white cells, 12,550; hemoglobin 11.8; neutrophils 70 per cent, lymphocytes 27 per cent, monocytes 2 per cent, eosinophils 1 per cent. The blood Kahn test was negative and the urinalysis gave normal findings. The Mantoux tests were negative with a dilution of 1:100 of PPD. Six sputum analyses and four gastric washings revealed no tubercle bacilli. The bleeding time was three minutes, clotting time 4.15 seconds, and the prothrombin time was 100 per cent of normal. Repeated sedimentation rate determinations were made and none exceeded 15 mm. per hour.

*X-ray findings:* The clinical improvement was checked by frequent X-ray examinations. Upon admission an X-ray film was taken at the bedside within six hours of onset of symptoms. There was a large area of density involving about one-half of the left thorax. A marked mediastinal shift to the right was evident. The findings were interpreted to indicate the presence of some fluid and a moderate degree of pneumothorax of the right lung. Repeated X-ray examinations during the next month showed a rapid decrease in the amount of fluid in the left thorax. The mediastinum gradually resumed its normal position. A final X-ray film taken shortly before discharge from the hospital shows that the fluid had completely disappeared and the chest was clear except for slight pleural thickening over both apices.

#### DISCUSSION

Hemopneumothorax occurring spontaneously and suddenly in seemingly healthy persons is a definite entity and should not be confused with cases of hemothorax occurring in the course of tuberculosis or those caused by trauma. The total number of cases remains small. A careful review of the literature reveals about 60 recorded cases. However, this may well be a misleading figure as to the incidence of the disease. It is very likely that many other cases exist but have not been reported.

Our case favors the opinion that conservative treatment is advisable and that aspiration, except for diagnostic purposes, is unnecessary unless severe cardiac or respiratory embarrassment occurs. If the patient survives the initial shock caused by the sudden hemorrhage the prognosis is good. Even large quantities of blood will absorb in a surprisingly short time, leaving no appreciable degree of pleural thickening. Final X-ray examination in our case showed slight thickening of the pleura over both apices. The question whether this was present before onset or represents a residual after-effect remains unanswered.

Most authors have agreed that, when aspiration is performed in cases of hemopneumothorax, a dark bloody fluid is obtained which fails to clot upon standing. The presence of such fluid occasionally, however, accompanied by clots, has also been confirmed in those cases which came to autopsy. In our case 60 cc. of fluid resembling blood which did not clot upon standing sixty minutes was removed. Pitt (11), in his description of the first case, emphasized the importance of this phenomenon. He disagreed with a suggestion made by Pagensticker (10) that the pleural cavity was capable of keeping blood fluid in a manner similar to blood vessels. Pitt pointed out that Trousseau (15) had

concluded that the extravasated blood did clot but that defibrination had taken place and was caused by respiratory and cardiac movements. Most authors since have agreed that the bloody fluid withdrawn is actually defibrinated blood. Recently Sellors (14) pointed out that a considerable dilution by pleural exudate takes place.

The question of the existence of an anticoagulant in the pleural exudate was raised by Zahn and Walker (16). They introduced 5 to 8 cc. of blood into the pleural cavity, removed this ten to twenty minutes later, and found it to be fluid which failed to clot upon standing. Their conclusion was that fibrinogen was in some way altered or destroyed by the pleural surfaces. Minot and Denny (1) repeated these experiments and described the presence of small blood clots as well as fluid blood. When pure fibrinogen was introduced into the pleural cavity it was not altered. They concluded that no anticoagulant existed, that blood did clot and was defibrinated by mechanical action.

The exact fate of the fibrin is obscure. In several cases which came to autopsy, masses of fibrin deposit were found covering the pleural surfaces. When smaller amounts were produced and the patient survived, often no clinical or X-ray evidence of pleural coating could be found. Our case seems to fall into this group.

The possibility of a fibrinolytic enzyme has been suggested. Quick (12), summarizing the work of Morawitz (9), Lengenhager (8) and others, postulates its presence in the pleural cavity. A fibrinolytic enzyme has been found to exist in other parts of the body. Rossenmann (13) isolated an active preparation of fibrinolysin from a pneumonic lung. He found the enzyme to be thermolabile and inactive in a 0.4 per cent solution of sodium bicarbonate. Huggins (4,5,6) and collaborators found a protease present in menstrual fluid capable of dissolving clots of peripheral blood. They also found a fibrinolytic enzyme present in human semen. It remains an interesting problem whether a similar phenomenon is responsible for the apparent disappearance of fibrin deposited on the pleural surface.

#### SUMMARY

1. A case of spontaneous hemopneumothorax occurring in an apparently well 26 year old white male is described.

2. The physiological mechanisms responsible for blood remaining in a fluid state while in the pleural cavity have been briefly discussed. The reports suggesting the presence of a fibrinolytic enzyme have been summarized.

#### SUMARIO

1. Descríbese un caso de hemoneumotórax espontáneo en un varón blanco aparentemente sano, de 26 años de edad.

2. Repásanse sucintamente los mecanismos fisiológicos que mantienen la sangre en estado líquido mientras permanece en la cavidad pleural. Sumarízanse las comunicaciones que indican la presencia de una encima fibrinolítica.



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# THE RELATION BETWEEN CHEMICAL STRUCTURE OF SULFONES AND THEIR BACTERIOSTATIC ACTIVITY<sup>1</sup>

*In Vitro* Studies with Virulent Human Type Tubercle Bacilli

GUY P. YOUMANS<sup>2</sup> AND LEONARD DOUB<sup>3</sup>

A number of derivatives of 4,4'-diaminodiphenylsulfone have been tested for their therapeutic effect on infections caused by human type tubercle bacilli. Feldman and his collaborators (1, 2, 3, 4) and others (5, 6, 7) have shown that some of these compounds exert a marked suppressive effect on experimental tuberculosis of the guinea pig whereas others are inactive. Derivatives such as promin, promizole and diasone have on the whole given disappointing results when used clinically (8).

A number of these compounds have also been tested *in vitro* for their bacteriostatic action on virulent human type tubercle bacilli and have been found to vary in their ability to inhibit growth (7, 9, 10, 11).

There has been no systematic study, however, either *in vivo* or *in vitro*, on the relation between the chemical structure of the 4-aminophenyl sulfones and their ability to inhibit growth of virulent human type tubercle bacilli. Such a study would be of value in that it might point the way to the development of derivatives more active than those already in use and, further, would permit a comparison of the bacteriostatic power of these compounds *in vitro* with their ability to suppress experimental tuberculosis in laboratory animals.

## METHODS

The method used for testing the bacteriostatic activity of the sulfones *in vitro* has been published previously by Youmans (9). Potassium sulfate was substituted for the magnesium sulfate in the synthetic medium since this eliminated the formation of a precipitate on autoclaving. All dilutions of the compounds and the control tubes were inoculated with 0.1 mg. of a fine suspension of the H37Rv strain of *M. tuberculosis*. These tubes were incubated at 37°C. and the results read at the end of fourteen days. The tubes were not shaken at any time during the period of incubation. The least amount of the compounds which completely prevented subsurface growth of the tubercle bacilli was recorded as the bacteriostatic endpoint.

Heat stable compounds were autoclaved in the medium after being diluted. Unstable compounds were sterilized by Berkefeld filtration and then diluted aseptically.

Since for reasons previously published (9) the bacteriostatic endpoints may vary from time to time, a series of dilutions of 4,4'-diaminodiphenylsulfone was

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included in every set of determinations to permit comparison of results obtained at different times by calculation of the 4,4'-diaminodiphenylsulfone coefficients (9). This was done by dividing the inhibiting molar concentrations of 4,4'-diaminodiphenylsulfone by the inhibiting molar concentrations of the other compounds. For convenience in appraisal these coefficients as given in the tables have been multiplied by 100.

Since the method employed, as shown by experience, carries an inherent error of a plus or minus one dilution, the coefficients of the compounds should be four times greater than or one-fourth as great as that of 4,4'-diaminodiphenylsulfone in order to be considered significantly different in their bacteriostatic activity. Actual experience, however, has shown that in many cases smaller differences are significant.

*Source of compounds:* We are indebted for compounds numbers 12 and 26 to Dr. W. H. Feldman, Mayo Foundation, Rochester, Minnesota; for compounds 7 and 8 to Dr. Henry Gilman, Iowa State College, Ames, Iowa; to Dr. H. B. Cutter, Wayne University, Detroit, Michigan, for compound number 4; for compound number 25 to Dr. L. P. Kyrides, Monsanto Chemical Company, St. Louis, Missouri; for the majority of the remaining compounds<sup>4</sup> to Dr. L. L. Bambas, Mr. B. F. Tullar, Dr. C. K. Banks and Mr. A. L. Rawlins, Research and Biological Laboratories, Parke, Davis and Company, Detroit, Michigan.

## RESULTS

The results of the bacteriostatic tests with derivatives of 4,4'-diaminodiphenylsulfone are tabulated in tables 1 to 5.

Modification of the sulfone linkage (table 1) reduced the bacteriostatic activity for *M. tuberculosis*, with one exception, compound number 6. This compound was at least equal to, and possibly more effective than, the reference substance.

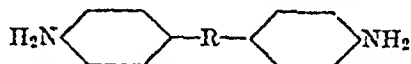
Replacement of one amino group by other substituents in various positions (table 2) also resulted in reduced bacteriostatic activity, with the possible exception of compound number 11. This compound is rather easily reduced to 4,4'-diaminodiphenylsulfone; so its activity may possibly be explained on this basis (12). Compounds 9 and 14, because of their low solubility, could not be tested in concentrations greater than 2.5 mg. per cent. Therefore, the high maximal coefficients listed for these compounds are possibly misleading.

Results obtained when substitutions were made in the amino groups are shown in table 3. Substitution of one or both amino groups with a stable acyl group markedly reduced the activity (compounds 15, 16, 17, 22, 23, 24, 25). Compound 19 and possibly 22 appear exceptional in this respect. Monoalkylation did not affect activity with compound 21 and decreased activity with numbers 18 and 20. Symmetrical dialkylation destroyed activity completely (number 26) in the single example available for test. Compounds 27 and 28 are both

<sup>4</sup> Papers are in preparation giving the chemistry of the new compounds included in this paper.

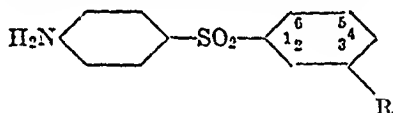
easily hydrolyzed under conditions of the *in vitro* test and their activity may be due to the resulting 4,4'-diaminodiphenylsulfone.<sup>5</sup>

TABLE 1  
4,4'-diaminodiphenylsulfone derivatives  
Modification of the sulfone linkage



NUMBER OF COMPOUND	REPLACEMENT	BACTERIOSTATIC CONCENTRATION IN MG. PER CENT		4,4'-DIAMINODIPHENYLSULFONE COEFFICIENT $\times 100$
		Compound	4,4'-diaminodiphenylsulfone	
1	—SO <sub>2</sub> —			100.0
2	—SO—	>10.0	0.625	<5.6
3	—COCO—	5.0	0.312	6.0
4	—SO <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> SO <sub>2</sub>	>10.0	1.25	<21.0
5	—S—	5.0	1.25	22.0
6	—SO <sub>2</sub> S—	0.156	0.312	220.0

TABLE 2  
4,4'-diaminodiphenylsulfone derivatives  
Replacement of one amino group by other substituents in various positions

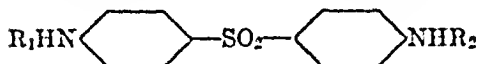


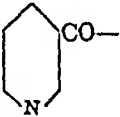
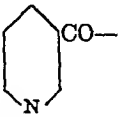
NUMBER OF COMPOUND	REPLACEMENT	BACTERIOSTATIC CONCENTRATION IN MG. PER CENT		4,4'-DIAMINODIPHENYLSULFONE COEFFICIENT $\times 100$
		Compound	4,4'-diaminodiphenylsulfone	
7	4—CH <sub>3</sub>	>10.0	0.625	<6.2
8	2—CH <sub>3</sub>	5.0	0.625	12.5
9	4—N <sub>3</sub>	>2.5	1.25	<55.0
10	4—OH	>10.0	0.625	<6.2
11	4—NO <sub>2</sub>	0.625	0.312	55.0
12	4—CH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> S—	>10.0	0.312	<4.0
13	3—NH <sub>2</sub>	>10.0	1.25	<12.5
14	2—NH <sub>2</sub>	>2.5	1.25	<50.0

Nuclear substitution (table 4) in one ring appeared to lower the bacteriostatic activity except for compound 43. With many of the compounds, however, the

<sup>5</sup> The ready formation of some free amino compound can be easily demonstrated even in fresh solution of these compounds by diazotization and coupling with dimethyl  $\alpha$  naphthylamine whereby a strong color is developed.

TABLE 3  
 4,4'-diaminodiphenylsulfone derivatives  
 Substitution of the amino groups



NUMBER OF COMPOUND	REPLACEMENTS		BACTERIOSTATIC CONCENTRATION IN MG. PER CENT		4,4'-DIAMINO-DIPHENYLSULFONE COEFFICIENT X 100
	1	2	Compound	4,4'-diaminodiphenyl-sulfone	
15		H	>10.0	0.625	<8.9
16	HO <sub>2</sub> CCH <sub>2</sub> CH <sub>2</sub> CO—	H	>10.0	0.625	<8.8
17	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> CO—	H	>10.0	0.312	<5.4
18	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> CH <sub>2</sub> —	H	>10.0	0.312	<5.2
19	CH <sub>3</sub> CO—	H	10.0	2.5	29.5
20	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub> —	H	2.5	0.625	29.0
21	—CH <sub>2</sub> CH=CH <sub>2</sub>	H	2.5	2.5	115.0
22	CH <sub>3</sub> CO—	Same as R <sub>1</sub>	>10.0	1.25	<16.7
23		Same as R <sub>1</sub>	>10.0	0.312	<5.7
24	NaO <sub>2</sub> CCH <sub>2</sub> CH <sub>2</sub> CO—	Same as R <sub>1</sub>	>10.0	0.625	<14.8
25	NaO <sub>2</sub> CCH <sub>2</sub> —S—CH <sub>2</sub> CO—	Same as R <sub>1</sub>	>10.0	0.312	<7.0
26	CH <sub>3</sub> —	Same as R <sub>1</sub>	>10.0	0.312	<3.5
27	CH <sub>2</sub> OH(CHOH) <sub>4</sub> C(SO <sub>3</sub> Na)—	Same as R <sub>1</sub>	2.5	0.312	39.0
28	CH <sub>3</sub> C(SO <sub>3</sub> Na)—	Same as R <sub>1</sub>	1.25	0.312	51.1

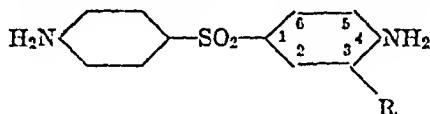
indicated reduction in activity is so slight that they actually may not be significantly less bacteriostatic than 4,4'-diaminodiphenylsulfone.

With the exception of compound 59, all of the heterocyclic analogues of 4,4'-diaminodiphenylsulfone (table 5) are less active *in vitro* than the parent

substance. The bacteriostatic power of many of these, however, is close to the of 4,4'-diaminodiphenylsulfone (compounds 49, 50, 51, 55, 56, 58). All of these latter compounds are isosteric with corresponding 4,4'-diaminodiphenylsulfone derivatives. Of the inactive compounds, number 47 is not isosteric with 4,4'-diaminodiphenylsulfone. Compound 48 is not isosteric with 4,4'-diaminodiphenylsulfone but its low solubility prevented a true evaluation of its bacteriostatic activity. Compounds 52, 53, 54, 57 and 58 show the effect of substitution of the amino group on compound number 50 and its derivative compound

TABLE 4

4,4'-diaminodiphenylsulfone derivatives  
Nuclear substitution in one phenyl ring



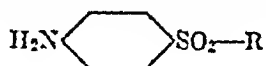
NUMBER OF COMPOUND	REPLACEMENT	BACTERIOSTATIC CONCENTRATION IN MG. PER CENT		4,4'-DIAMINODI- PHENYLSULFONE COEFFICIENT X 100
		Compound	4,4'-diaminodi- phenylsulfone	
29	2-SO <sub>2</sub> NH <sub>2</sub>	10.0	0.625	8.2
30	2-SO <sub>2</sub> NNaCOCH <sub>3</sub>	>10.0	2.5	<39.5
31	2-SO <sub>2</sub> NNaCOCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	5.0	0.625	20.0
32	2-SO <sub>2</sub> H	>10.0	0.625	<8.2
33	3-SO <sub>2</sub> NH <sub>2</sub>	2.5	0.625	32.0
34	3-SO <sub>2</sub> H	>10.0	0.625	<8.2
35	3-NH <sub>2</sub>	5.0	0.625	13.0
36	2-NH <sub>2</sub>	>10.0	2.5	<26.0
37	3-Cl	>2.5	1.25	<57.0
38	2-Cl	5.0	2.5	57.0
39	3-CH <sub>3</sub>	5.0	2.5	52.8
40	2-CH <sub>3</sub>	2.5	1.25	53.0
41	2-OH	1.25	0.312	26.5
42	2-SO <sub>2</sub> NH <sub>2</sub> , 5-CH <sub>3</sub>	>10.0	0.625	<8.6
43	2-CH=NOH	0.312	0.625	230.0
44	3-SO <sub>2</sub> NH <sub>2</sub> , 6-CH <sub>3</sub>	2.5	0.625	34.0
45	2-NH <sub>2</sub> , 4-CH <sub>3</sub>	>10.0	2.5	<28.0
46	2-NH <sub>2</sub> , 5-CH <sub>3</sub>	10.0	2.5	28.0

number 56. They behaved in a manner similar to the analogous derivatives of 4,4'-diaminodiphenylsulfone.

#### DISCUSSION

The limited nature of this study permits only restricted generalization of the relation of structure to bacteriostatic activity. Maximum activity in the diaminodiphenylsulfone moiety seems contingent upon the presence of two para-oriented free amino groups. Replacement of one amino group by methyl (compound 7) and butyl thio (compound 12), or transfer of the amino group to the meta and possibly ortho positions (compounds 13 and 14) gives relatively

TABLE 5  
*p*-aminophenyl heterocyclic sulfones



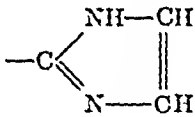

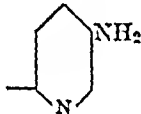
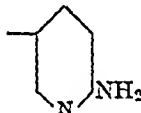
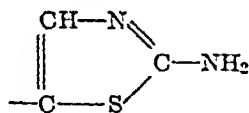
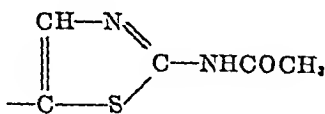
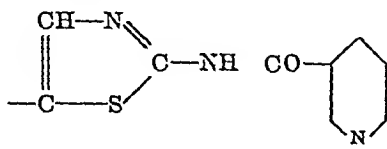
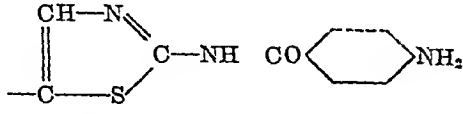
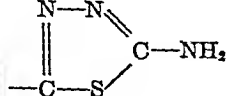
NUMBER OF COMPOUND	REPLACEMENT	DIACTRIOSTATIC CONCENTRATION IN MG. PER CENT		4,4'-DIAMINO- DIPHENYL- SULFONE COEF- FICIENT $\times 100$
		Compound	4,4'-diamino- diphenyl sulfone	
47		>10.0	0.625	<5.4
48		>2.5	1.25	<47.0
49		5.2	0.625	12.5
50		10.0	2.5	25.0
51		1.25	0.312	26.0
52		>10.0	0.625	<7.4
53		>10.0	2.5	<37.8
54		>10.0	2.5	<37.6
55		5.0	0.625	13.0

TABLE 5—*Concluded*

NUMBER OF COMPOUND	REPLACEMENT	BACTERIOSTATIC CONCENTRATION IN MG. PER CENT		4,4'-DIAMINO-DIPHENYL-SULFONE COEFFICIENT X 100
		Compound	4,4'-diaminodiphenyl sulfone	
56	$\begin{array}{c} \text{CH}_3-\text{C}-\text{N}=\text{C}-\text{NH}_2 \\ \parallel \quad \diagdown \\ -\text{C}-\text{S} \end{array}$	5.0	0.625	13.9
57	$\begin{array}{c} \text{CH}_3-\text{C}-\text{N}=\text{C}-\text{NHCH}=\text{CHCH}_3 \\ \parallel \quad \diagdown \\ -\text{C}-\text{S} \end{array}$	5.0	0.312	7.7
58	$\begin{array}{c} \text{CH}_3-\text{C}-\text{N}=\text{C}-\text{NHCH}_3 \\ \parallel \quad \diagdown \\ -\text{C}-\text{S} \end{array}$	1.25	0.625	56.0
59	$\begin{array}{c} \text{CH}-\text{N}-\text{CH}_3 \\ \parallel \quad \diagdown \\ -\text{C}-\text{S} \quad \text{C}=\text{NH} \end{array}$	0.625	0.625	110.0

inactive derivatives. Alkylation of only one amino group in compounds 18 and 20, though confirming the desirability of having both amino groups free, leaves enough activity with number 20 to suggest that this type of substitution may be exceptional. All other amino substituted compounds, where stable under conditions of the test, (compounds 15, 16, 17, 19, 22, 23, 24, 25, 26) showed greatly reduced activity. Activity does not depend upon both rings remaining unsubstituted; several compounds (numbers 33, 38, 39, 40, 41, 43, 44 and 46) containing an additional group attached to one phenyl ring retain activity. One phenyl group may be replaced by a heterocyclic ring which retains the same relative position of the amino and sulfone groups.

The isosteres of 4,4'-diaminodiphenylsulfone derivatives (table 5) constitute a chemical group distinct from that compound. The number of this type available for study is limited but the few examples available suggest that they follow the same general trends of activity outlined above for derivatives of 4,4'-diaminodiphenylsulfone. Activity seems incompatible with acylation of the heterocyclic amino group; acylation of compound 51 results in loss of activity (compounds 52 and 53). Substitution into the heterocyclic ring (compounds 56, 57, 58, 59) does not completely destroy activity. Also, as noted with diaminodiphenylsulfone derivatives, substitution of one amino group with an alkyl residue (compounds 57 and 58) does not always destroy activity.

Thus it appears possible that for p-aminophenyl sulfones in general the presence of a second unsubstituted amino group is not essential for bacteriostatic



activity against the tubercle bacillus, providing the substituent is an alkyl group. In view of the ready metabolism of some alkylamino compounds by biological systems (13, 14, 15), however, even here activity may be due to the corresponding free amino compound; in this instance the tubercle bacillus itself may produce the active agent. This contrasts with the inactivity of the corresponding acylamino derivatives which would not appear to be metabolized to the parent amino compound.

An alternative postulation which would harmonize the data of this study may be derived from the fact that, whereas acylation destroys the basic nature of the amino group, monoalkylation actually enhances this property. Thus, all the more active p-aminophenyl sulfones included in this study possess a second basic centre in the para position in the second phenyl ring or in an equivalent position in a heterocyclic ring. This may be a necessary condition for maximum activity against the tubercle bacillus and would include the special case mentioned above in which the test organism might itself produce the active compound. In this latter instance the second basic centre would become simply the amino group itself.

#### SUMMARY

Fifty-nine sulfone compounds were tested *in vitro* for their bacteriostatic activity for the virulent human type tubercle bacillus H37Rv. The relationship between the chemical structure of these compounds and their tuberculostatic activity is discussed.

#### SUMARIO

Cincuenta y nueve compuestos de la sulfona fueron ensayados *in vitro* en cuanto a actividad bacteriostática para el bacilo tuberculoso de tipo humano virulento H37Rv. Discútese aquí la relación entre la composición química de dichos productos y su actividad bacteriostática.

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# A COMPARISON OF THE EFFECT OF P-AMINO PHENYL SULFONE COMPOUNDS IN VITRO AND IN VIVO ON TUBERCLE BACILLI

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The testing of chemotherapeutic agents for their ability to suppress infections produced by *M. tuberculosis var. hominis* in guinea pigs is laborious and time-consuming. The nature of the tubercle bacillus and the course of the disease it produces are such that the test period must be as long as two to six months. Furthermore the amount of a compound necessary to administer to guinea pigs for this period of time frequently taxes the resources of the chemist.

There is, therefore, an urgent need for a more rapid preliminary screening procedure to be used primarily for the purpose of eliminating inactive compounds.

*In vitro* tests for the bacteriostatic activity of compounds against the tubercle bacillus have been utilized by a number of investigators. Many of these experiments, however, have been done under conditions which would tend to mask the bacteriostatic activity of the substances being tested. Furthermore no tests have been done on a closely related series of chemical compounds of demonstrated activity in suppressing experimental tuberculosis in laboratory animals. There is, therefore, no clear-cut evidence that an *in vitro* screening procedure would serve the primary purpose of eliminating compounds inactive against the tubercle bacillus, although this procedure has been recommended for the testing of chemotherapeutic agents for other bacteria (1).

The development by Young (2) of a rapid and reasonably accurate *in vitro* bacteriostatic testing method, using subsurface growth of virulent human type tubercle bacilli under conditions which favor the action of the substances being tested, furnished an opportunity to determine the validity of a preliminary *in vitro* procedure by a comparison with the extensive *in vivo* tests carried out by Feldman and his coworkers (3 to 6).

The compounds reported in this paper have been purposely limited to the p-aminophenyl sulfones since many of these compounds are effective in suppressing experimental tuberculosis in guinea pigs. This furnished an opportunity to determine the relationship between *in vitro* and *in vivo* bacteriostatic tests with virulent human type tubercle bacilli.

## METHODS

The method for testing, *in vitro*, the bacteriostatic activity of the compounds against virulent human type tubercle bacilli has been previously described (2). Only those compounds which inhibited subsurface growth of the tubercle bacillus

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TABLE 1  
The effect in vitro and in vivo of *p*-amino phenyl sulfone compounds on  
*M. tuberculosis*

NUMBER OF COMPOUND		ACTION IN VITRO	ACTION IN VIVO
M-1	Sodium 4,4'-diaminodiphenylsulfone-N,N'-di-(dextrose sulfonate)*	+	+
M-3	4,4'-diamino-2-acetylsulfamyl diphenyl sulfone†	+	—
M-4	4-Amino-4'-dodecanoylamino diphenyl sulfone	—	—
M-5	4-Amino-4'-succinylamino diphenyl sulfone‡	+	+
M-6	4-Aminophenyl-5'-amino-2'-pyridyl sulfone	+	—
M-7	4,4'-bis succinylamino diphenyl sulfone	—	—
M-8	4,4'-diaminodiphenylsulfone	+	+
M-10	4-Amino-4'-propylamino diphenyl sulfone	+	+
M-11	4-(2'',5''-Dimethyl-N-pyrryl)-4'-succinylamino diphenyl‡ sulfone	—	—
M-12	2,4'-Diamino-5'-thiazolyl phenyl sulfone§	+	+
M-13	4,4'-Diamino-3-methyl diphenyl sulfone	+	+
M-14	4,4'-bis (thiodiglycolylamino) diphenyl sulfone	—	—
M-16	4-Amino-4'-nicotinylamino diphenyl sulfone	+	+
M-21	4-Aminophenyl-2'-amino-4'-methyl-5'-thiazolyl sulfone	+	+
M-22	4-Aminophenyl-2'-amino-5'-thiodiazolyl sulfone	+	—
M-23	4,4'-Diaminodiphenylsulfoxide†	—	+
M-24	4,4'-Diamino benzil†	+	+
M-25	4,4'-Diamino-2-propionylsulfamyl diphenyl sulfone‡	+	—
M-26	4-Aminophenyl-2'-acetylamino-5'-thiazolyl sulfone	—	+
M-32	4-Aminophenyl-2'-amino-3'-methyl-Δ <sup>2</sup> -thiazolonyl-5'-sulfone	+	+
M-34	4-Aminophenyl-2'-methylamino-4'-methyl-5'-thiazolyl sulfone	+	—
M-37	4-Aminophenyl-2'-allylamino-4'-methyl-5'-thiazolyl sulfone	+	—
M-38	4-Aminophenyl-2'-nitro-5'-thienyl sulfone	+	—
M-39	4,4'-Diamino-2-chloro diphenyl sulfone	+	—
M-40	2,4,4'-Triamino diphenyl sulfone	—	—
M-44	4-Aminophenyl-2'-nicotinylamino-5'-thiazolyl sulfone	—	—
M-45	4-Aminophenyl-2'-(4''-aminobenzamido)-5'-thiazolyl sulfone	—	—
M-49	4-Aminophenyl-2'-amino-5-pyridyl sulfone	+	+
M-52	4-Amino-4'-allylamino diphenyl sulfone	+	+
X-1	4-Amino-4'-n-butylthio diphenyl sulfone	—	—
X-2	4,4'-bis n-butylthio diphenyl sulfone	—	—
X-3	4,4'-bis methylamino diphenyl sulfone	—	+
X-4	Sodium 4,4'-diaminodiphenylsulfone-N,N'-di (formaldehyde sulfoxylate)	+	+

\* Promin.

† These compounds though not sulfones bear sufficient structural resemblance to that type to justify inclusion here.

‡ These compounds tested as the sodium salts.

§ Promizole.

|| Diasone.

in concentrations of 10.0 mg. per cent or less were considered active. The *in vivo* chemotherapeutic tests were carried out in guinea pigs as recommended by Feldman and Hinshaw (7), and were based on survival time and the amount of parenchymal tuberculosis in spleen, liver and lungs. A compound was considered active *in vivo* against tubercle bacilli when definitive results indicative of deterrent action were observed in at least 4 out of 6 infected animals. Six was the minimal number of animals used in the preliminary screening tests. The H37Rv strain of *M. tuberculosis var. hominis* was used for both the *in vitro* and *in vivo* tests.

### RESULTS

The results obtained both *in vitro* and *in vivo* are given in table 1. No attempt was made to indicate the degree of activity either *in vitro* or *in vivo*, since, so far as we have been able to determine, there is frequently no quantitative relationship between the two.

An examination of table 1 shows that with 22 of the 33 compounds a correlation exists between the *in vivo* and *in vitro* tests. That is, both tests were either positive or negative for the same compound. Of the 11 remaining compounds, 8 were bacteriostatic *in vitro* but were ineffective *in vivo*. Only 3 of the compounds were active *in vivo* but inactive *in vitro*.

### DISCUSSION

White, Bratton, Litchfield and Marshall (1), in a study of the effect of 126 compounds *in vitro* and *in vivo* on  $\beta$ -hemolytic streptococci, found that no compound was effective *in vivo* if it was inactive *in vitro* unless it was a compound that could be decomposed *in vivo* to a compound that would be active *in vitro*. Furthermore, many compounds active *in vitro* were inactive *in vivo*.

The data given in table 1 show that the same generalizations hold for the effect of the sulfones on *M. tuberculosis in vivo* and *in vitro*. Only 3 compounds that were active *in vivo* were inactive *in vitro* (M-23, M-26, X-3). Compound M-23 is capable of being oxidized in the body to 4,4'-diaminodiphenylsulfone; M-26 can be hydrolyzed to the active compound M-12; and X-3 can be demethylated to 4,4'-diaminodiphenylsulfone.

Eight compounds active *in vitro* were inactive *in vivo*. All substances active *in vitro* will not necessarily be active chemotherapeutic agents *in vivo*, since one or more of the following factors may operate to prevent their activity. (1) Lack of absorption or too rapid excretion may result in too low a concentration in the body to give therapeutic results. (2) The toxicity of the drug may be too great. (3) The drug may be rapidly conjugated or destroyed in the body. (4) The compound may be inactivated by body fluids or tissues.

The results indicate that the preliminary *in vitro* testing for bacteriostatic activity, if the results are properly evaluated, may be of value for the elimination of inactive compounds. It should be emphasized, however, that the *in vitro* tests should be conducted under conditions that favor the bacteriostatic action of the compound. A synthetic medium should be used since a complex highly

nutrient medium may contain substances which antagonize or inactivate the test substance, or growth of the organism may be so stimulated that slight bacteriostatic activity of a compound will be obscured. Furthermore, since the bacteriostatic activity of many substances is inversely proportional to the number of organisms present, a uniform, relatively small inoculum of tubercle bacilli should be employed. The importance of the above factors in conducting *in vitro* bacteriostatic tests has been demonstrated in investigations on the mode of action of the sulfonamides (8).

Since all compounds active *in vivo* were also active *in vitro* unless they could be decomposed *in vivo* to compounds that would be active *in vitro* the results also support the thesis that the sulfone drugs act directly upon the bacterial organism when suppressing experimental infections caused by *M. tuberculosis*.

#### SUMMARY

Thirty-three sulfone type compounds were tested *in vitro* for their bacteriostatic activity against virulent human type tubercle bacilli and also *in vivo*, using the same virulent strain of tubercle bacillus, for their ability to suppress experimental tuberculosis in the guinea pig. All compounds that were effective *in vivo* were also bacteriostatic *in vitro*, except for 3 compounds that could be decomposed *in vivo* to compounds that would be active *in vitro*.

Eight compounds were active *in vitro* but were inactive *in vivo*.

The significance of these results is discussed.

#### SUMARIO

A 33 compuestos del tipo de la sulfona se les comprobó *in vitro* en cuanto a su actividad bacteriostática contra los bacilos tuberculosos de tipo humano virulento, y también *in vivo*, usando la misma cepa virulenta del bacilo, en cuanto a su capacidad para suprimir la tuberculosis experimental en el cobayo. Todos los compuestos que resultaron eficaces *in vivo* fueron también bacteriostáticos *in vitro*, salvo por 3 que podían descomponerse *in vivo* en compuestos activos *in vitro*.

Ocho compuestos mostráronse activos *in vitro*, pero inactivos *in vivo*.

Discútese la importancia de estos resultados.

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# ANTIMONY COMPOUNDS IN TUBERCULOSIS<sup>1,2</sup>

Their Effect on Experimental Tuberculosis in Guinea Pigs.

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In a group of Puerto Rican patients suffering from Bancroftian filariasis, who were treated with large doses of an organic antimonial compound, neostibosan (1), one patient, aged 20, developed moderately advanced pulmonary tuberculosis with a positive sputum a few weeks after completing a course of therapy in which 9.4 g. of the drug were given intravenously over a period of fifty-four days. Since the incidence of pulmonary tuberculosis is high in Puerto Rico the onset of the disease in this patient may well have been merely coincidental with the administration of antimony; but the possibility that the drug might have exercised a deleterious effect upon a preëxisting quiescent tuberculous infection had also to be considered.

Napier (2), who has had a wide experience with antimonial drugs in the treatment of leishmaniasis, states that he has frequently observed a detrimental action of antimony in phthisis and makes the following comment: "There is one disease in which antimony seems to exert a malign influence, namely, pulmonary tuberculosis. We have frequently observed that, when kala-azar and pulmonary tuberculosis co-exist, antimony has little or no effect on the symptoms—fever and splenic enlargement—and that, on the other hand, the lung lesions undergo rapid extension when antimony is given." Other investigators, however, have failed to note similar harmful results of antimonial treatment, and indeed Struthers (3), employing neostibosan extensively for the treatment of kala-azar among Chinese, has reported that those patients with tuberculosis of the lungs improve, as a rule, when given organic preparations of antimony. Unfortunately, the literature does not contain any other references of note which bear on this problem, and it is astonishing to discover that no adequate experimental observations on the effect of antimonial compounds on tuberculosis have hitherto been published. Since the only effective method of therapy in Bancroftian filariasis known at the present time consists of the very intensive administration of antimonial drugs, especially neostibosan, it seemed worth while to conduct a controlled study in order to observe whether these drugs actually do significantly modify a tuberculous infection in the experimental animal, and in this way possibly to determine whether such therapy may be potentially hazardous to the individual suffering from latent or manifest pulmonary tuberculosis.

## EXPERIMENTAL

Twenty-eight guinea pigs were infected with tubercle bacilli by the subcutaneous inoculation of 1 mg. (wet weight) of strain H37, suspended in nutrient

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<sup>2</sup> The work described in this paper was done in part under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the College of Physicians and Surgeons, Columbia University.

broth, into the right groin. Twenty-nine days after infection, 20 of the animals were divided into four treatment groups, each of 5 animals, while the remaining 8 guinea pigs were set aside as untreated controls. Each group of 5 infected animals was treated with a different antimonial drug, and the same drug was simultaneously administered to 5 normal uninfected guinea pigs.

The drugs employed included two trivalent compounds—anthiomaline (Specia) and fuadin (Winthrop)—and two quinquevalent compounds—neostam (Burroughs Wellecome) and neostibosan (Winthrop). Injections were made once daily by the intraperitoneal route. All of the animals were weighed each day and the amount of the drug to be given was calculated accordingly, so that a constant daily dose in terms of milligrams of drug per kilogram of body weight was maintained for each compound. These doses were as follows: anthiomaline 40 mg. per kilo; fuadin 60 mg. per kilo; neostam 60 mg. per kilo; and neostibosan 100 mg. per kilo. Anthiomaline and fuadin were administered in solution as furnished by the manufacturers; neostam and neostibosan, supplied in the form of powder, were freshly dissolved in sterile distilled water before injection. The

TABLE 1

*Percentages of drug solutions, the antimony content of the drugs and the amounts of drug and antimony per milliliter of the solutions*

DRUG	PER CENT DRUG IN SOLUTION	PER CENT ANTIMONY IN DRUG	DOSE OF DRUG PER ML. IN GRAMS	DOSE OF ANTIMONY PER ML. IN GRAMS
Anthiomaline.....	6.0	16.5	.060	.010
Fuadin.....	6.3	13.5	.063	.0085
Neostam.....	5.0	30.0	.050	.015
Neostibosan.....	6.0	40.0	.060	.024

percentages of the drug solutions, the antimony content of the drugs, and the amounts of drug and antimony per milliliter of the solutions are given in table 1.

Injections were made for a period of twenty-one days, during which time any animals that died were autopsied and the findings noted. At the end of the three weeks of treatment, fifty days after infection, all of the surviving tuberculous guinea pigs were sacrificed and carefully examined with particular reference to the state of the inguinal lymph nodes proximal to the site of injection, the retroperitoneal lymph nodes, the liver, the spleen and the lungs. The degree of involvement of these structures in regard to their size, the number of lesions and the amount of caseation was estimated grossly and recorded either as negative (0), slight (1), moderate (2), marked (3) or very marked (4). At the same time specimens of tissue were removed from the liver and the lungs of each animal to be analyzed for antimony.

#### RESULTS

*Drug-treated normal guinea pigs:* All normal guinea pigs treated for three weeks with the four antimonial compounds tolerated the treatment well with the exception of one of the 5 that received anthiomaline. This animal lost weight and

became obviously ill on the sixteenth day of therapy and died shortly afterward, apparently from the effects of the drug. The remaining guinea pigs continued to appear healthy, retained their appetites and most of them gained weight.

From these results it seems reasonable to conclude that, with the possible

TABLE 2  
*Tuberculous involvement at autopsy*

DRUG	ANIMAL NUMBER	REGIONAL LYMPH NODES	RETROPERITONEAL LYMPH NODES	LIVER	SPLEEN	LUNGS	TOTAL SCORE	GROUP AVERAGE
Anthiomaline	153	3	3	4	4	0	14 <sup>a</sup>	15.2
	154	3	3	3	4	4	17 <sup>b</sup>	
	156	3	3	4	4	4	18	
	157	3	3	4	4	1	15	
	173	3	2	3	3	1	12	
Fuadin	158	2	2	4	3	1	12	10.8
	159	2	2	2	1	1	8	
	160	2	1	2	2	1	8	
	161	2	3	4	4	3	16	
	162	2	1	3	3	1	10	
Neostam	164	1	1	4	4	2	12	11.4
	165	1	1	2	1	3	8	
	166	2	1	4	4	2	13	
	167	1	1	4	4	2	12	
	174	2	1	4	3	2	12	
Neostibosan	168	2	2	4	4	3	15	9.2
	169	1	1	1	3	1	7	
	170	0	0	2	1	0	3 <sup>c</sup>	
	171	3	2	0	2	2	9	
	172	2	1	4	4	1	12	
Control	175	2	1	4	4	3	14	15.4
	176	2	3	4	4	1	14	
	177	4	2	4	4	2	16	
	178	2	1	4	3	0	10	
	179	4	3	4	4	3	18	
	180	4	3	4	4	3	18	
	181	4	4	4	4	3	19	
	182	3	3	3	4	1	14	

a = Animal died on seventh day of treatment.

b = Animal died on nineteenth day of treatment.

c = Animal died on eleventh day of treatment.

exception of anthiomaline, the doses of the drugs that were chosen for administration were well within the limits of tolerance.

*Drug-treated tuberculous guinea pigs:* The tuberculous guinea pigs clinically tolerated the antimonial treatment somewhat less well than did the normal



animals. The majority of them lost moderate amounts of weight, exhibited a diminished appetite and became rather listless and apathetic. Two guinea pigs died during the course of therapy with anthiomaline, presumably because of toxic effects of the drug, on the seventh and nineteenth days of treatment, respectively. A third animal, treated with neostibosan, died on the eleventh day, apparently from an intercurrent infection.

None of the 8 control animals died during the period of observation, and all of them remained clinically in good general condition despite the infection.

TABLE 3  
*Tissue analyses for antimony*

DRUG	ANIMAL NUMBER	DOSE ANTI-MONY PER KILO PER DAY	TOTAL MG. ANTI-MONY INJECTED	MG. ANTIMONY PER G. LUNG	AVERAGE MG. ANTIMONY PER G. LUNG	MG. ANTIMONY PER G. LIVER	AVERAGE MG. ANTIMONY PER G. LIVER	MG. ANTIMONY PER G. LUNG	MG. ANTIMONY PER G. LIVER
								MG. ANTIMONY INJECTED PER G. BODY WEIGHT PER DAY	MG. ANTIMONY INJECTED PER G. BODY WEIGHT PER DAY
Anthiomaline	154	6.6	51.5			.031			
	156	6.6	72.3	.001		.013	.019	0.15	2.9
	157	6.6	63.1	.001	.001	.011			
	173	6.6	47.4	.001		.010			
Fuadin	158	8.1	98.0	.002		.026			
	159	8.1	56.7	.002		.024			
	160	8.1	76.0	.002	.002	.034	.023	0.25	2.8
	161	8.1	75.2			.010			
	162	8.1	99.2	.002		.021			
Neostam	164	18.0	159.8	.008		.017			
	165	18.0	201.6	.009		.069			
	166	18.0	128.6		.008	.038	.062	0.45	3.4
	167	18.0	179.6	.008		.075			
	174	18.0	120.6	.007		.083			
Neostibosan	168	40.0	379.7	.035		.538			
	169	40.0	395.0	.064	.053	.494	.511	1.3	12.8
	171	40.0	356.6	.056		.555			
	172	40.0	234.0	.057		.470			

The necropsy findings in both the treated and the control groups are presented in table 2, according to the method previously described. The scores of involvement of the regional lymph nodes, the retroperitoneal lymph nodes, the liver, the spleen and the lungs were totalled for each animal. From these totals the average score for each group was calculated. It will be seen at once that the extent of the tuberculous disease in the four groups of guinea pigs treated with antimonial compounds in no case exceeded that seen in the control animals. Indeed, the disease was found to be significantly less extensive, on the average, in the groups treated with fuadin, neostam and neostibosan, suggesting that these drugs had actually exercised a slightly beneficial effect on the course of the

infection. The degree of tuberculous involvement in the animals given anthiomaline was almost identical with that observed in the controls.

*Antimony content of the lungs and livers of drug-treated tuberculous guinea pigs:* The analyses for antimony on specimens of lung and liver removed from the drug-treated animals at the time of necropsy were performed using a modification of the method described by Maren (4). Table 3 presents the milligrams of antimony injected per kilogram of body weight, the total milligrams of antimony injected into each animal, and the tissue antimony determinations expressed as concentrations of antimony per gram of lung and per gram of liver. The last two columns of the table show the ratios of the average antimony concentrations in the lung and liver to the daily doses of antimony injected per gram of body weight. The absolute values of the tissue antimony concentrations are revealing. As can be seen, the antimony levels in the lungs are lowest with the tervalent antimonials, anthiomaline and fuadin, somewhat greater in the experiments with neostam, and relatively large in the animals receiving neostibosan; however, in every case the antimony concentration in the lungs is extremely small when compared with the total amount of antimony administered. The concentrations of antimony in the liver are very much higher than the antimony concentrations in the lung in all instances. As in the case of the lungs, the antimony concentration is greatest in the neostibosan experiments, lowest following the administration of anthiomaline and fuadin, and intermediate for neostam. The values relating the antimony concentrations in the lungs and liver to the daily doses of antimony injected were calculated in order to compare the degree of antimony cumulation of the four drugs. They indicate that the injection of neostibosan was accompanied by a retention of antimony which was proportionally four times as great as that obtained with any of the other three drugs.

#### DISCUSSION

The results obtained under the conditions of this experiment indicate that the administration of anthiomaline, fuadin, neostam and neostibosan to guinea pigs suffering from tuberculosis does not unfavorably modify the course of the disease in these animals. On the contrary, fuadin, neostam and neostibosan apparently have a slight but definite restraining influence on the infection.

If antimony itself exerted a deleterious effect on the tuberculous process, then one would expect such an effect to be caused most readily by neostibosan, administration of which results in high tissue concentrations of antimony. But it was found that the average extent of the disease in animals treated with this drug was the least of any of the groups studied. In fact, the circumstances suggest the possibility that the beneficial action of neostibosan, which was the greatest of any of the drugs tested, may be related to these high tissue concentrations of antimony.

It is difficult to reconcile these experimental findings with Napier's remarks on the fatal combination of pulmonary tuberculosis and antimonial therapy, although it must be borne in mind that other investigators have not confirmed Napier's clinical observations. It is quite possible that in patients who are

suffering from the advanced stages of a severe wasting disease, such as kala-azar, and who develop a concomitant tuberculous infection of the lungs, the administration of compounds of antimony, with the attendant side-reactions they may produce—such as anorexia, nausea and vomiting, among others—may worsen the prognosis. But this does not necessarily mean that an unfavorable issue should be specifically attributed to the action of antimony.

Our own experience in the treatment of nearly 100 cases of filariasis (5) with large doses of several antimonial compounds indicates that, on the whole, these drugs are very well tolerated. Our cases were all native Puerto Ricans, treated in an environment where pulmonary tuberculosis is much more prevalent than in the continental United States. Yet only one of these patients developed clinical manifestations of the disease which had any temporal relationship to the administration of the drug, and this was probably a coincidence of events. Moreover, one individual with X-ray evidence of minimal pulmonary tuberculosis endured intensive antimony therapy without any untoward incident. These observations, together with the experimental findings here presented, lead us to conclude that antimony therapy *per se* probably does not exercise an unfavorable influence on a tuberculous infection.

#### SUMMARY

Tuberculous guinea pigs were treated intensively with the antimony compounds anthiomaline, fuadin, neostam and neostibosan. The results indicated that antimony, thus administered, did not exert any deleterious effect on the course of the tuberculous infection in these animals.

#### SUMARIO

A cobayos tuberculosos se les trató intensamente con los compuestos antimoniales: antiomalina, fuadina, neostam y neostibosán, indicando los resultados que el antimonio, administrado en esta forma, no ejerce efecto nocivo sobre la evolución de la infección tuberculosa en dichos animales.

The authors wish to express their gratitude to Miss Elizabeth Pearce for technical assistance.

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## PASSIVE TRANSFER OF LOCAL ALLERGIC HYPERSENSITIVE- NESS TO TUBERCULIN<sup>1,2</sup>

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Within the past decade, the specific immunological and specific allergic phases of tuberculosis have been resolved into separate entities and have shown themselves insusceptible of passive transfer by means of the whole blood or any of its parts into normal recipient animals. On the other hand, tuberculin (tuberculo-protein), though of value for determining the existence of allergic hypersensitiveness to tuberculin, was found not to be liberated by the tubercle bacillus *in vivo*, nor to play any part in the animal or human economy in the manifestations of specific tuberculo-immunity nor in the specific tuberculo-allergy as it existed normally in tuberculous man or animals (1).

In 1940 (2), it was recorded that maximum growth of human tubercle bacilli occurs within two to three months on a simple synthetic nonprotein medium, while tuberculo-protein liberation into the medium takes place mainly after maximum growth is attained (3). These (4,5) and other prior observations led to the conclusion that tuberculin (tuberculo-protein) is a product of *in vitro* autolysis of tubercle bacilli—a product of enzymatic action. In 1943 (6), it was noted that there are four independent biological reactions to tubercle bacilli and their natural products which are important in the evaluation of tuberculosis. These are specific tuberculo-immunity, specific tuberculo-bacillary allergy, specific tuberculin allergy, and tuberculo-protein (tuberculin) anaphylaxis. Tuberculo-protein (tuberculin) anaphylactic hypersensitiveness is produced by tuberculo-protein (tuberculin), and lethal anaphylactic shock results from an intravenous injection of tuberculin two to three weeks after sensitization. Proper intravenous injections of tuberculo-protein (tuberculin) suffice to immunize against a lethal tuberculo-protein (tuberculin) anaphylactic shock. Passive transfer of citrated blood of tuberculin immune guinea pigs to normal animals prevents tuberculo-protein (tuberculin) sensitization to tuberculin anaphylactic shock. Passive transfer of citrated whole blood of immune or anaphylactic hypersensitive guinea pigs with or without the addition of tuberculo-protein (tuberculin) failed to protect tuberculin hypersensitive guinea pigs from the effects of the lethal tuberculin anaphylactic shock. It was noted earlier (7, 8) that bacillary sensitized or tuberculous animals do not respond to an injection of tuberculo-protein after an appropriate incubation period by an acute anaphylactic shock reaction but do reveal a protracted allergic intoxication with fatal issue to a suitable amount of tuberculo-protein. Tuberculo-protein sensitized guinea pigs do not develop an acute (anaphylactic) shock after the injection of washed young tubercle bacilli, while bacillary sensitized and tuberculous (allergic) animals succumb to these injections.

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<sup>2</sup> This investigation was aided by a gift from Morton May in memory of Florence G. May.

In 1942 (9) it was noted that tuberculo-anaphylactic hypersensitiveness in mother guinea pigs produced by tuberculo-protein is regularly transferred to offspring born for over a year after sensitization of the mother. Tuberculo-anaphylactic hypersensitiveness is not produced by tubercle bacilli or by tuberculosis. Tuberculo-allergic hypersensitiveness in tuberculous mother guinea pigs, produced by small infecting amounts of virulent human tubercle bacilli, is not transferred to the offspring.

An attempt (10) to desensitize tuberculo-bacillary allergic hypersensitive guinea pigs by means of viable avirulent tubercle bacilli resulted rather in an accentuation of the allergic hypersensitiveness. Heat-killed tubercle bacilli also were of no value so far as desensitization was concerned. In other tests with the offspring of heavily infected mothers (11), it was found that they do not develop any discernible specific tuberculo-allergic hypersensitiveness as tested by the skin tuberculin test. Even the administration of relatively large amounts of viable avirulent human tubercle bacilli given to mother guinea pigs and producing in them a definite specific tuberculo-allergic hypersensitiveness to tuberculin produces no evidence of transfer of the hypersensitiveness to the offspring.

In a recent phagocytic cell study (12), it was found that tuberculin (tuberculo-protein) is relatively innocuous to the phagocytic cells from normal guinea pigs, as measured by the phagocytosis of *Staphylococcus aureus* or human tubercle bacilli, and that it depresses the phagocytic blood cells of allergically tuberculin hypersensitive, anaphylactically tuberculin hypersensitive or tuberculous guinea pigs. This depression of phagocytosis is accentuated markedly if the allergically tuberculin hypersensitive or anaphylactically tuberculin hypersensitive guinea pigs have been treated previously with tuberculin or heat-killed tubercle bacilli. The depression of phagocytic activity of the phagocytic blood cells from allergically tuberculin hypersensitive, anaphylactically tuberculin hypersensitive or tuberculous guinea pigs, untreated or treated with tuberculin, does not appear to be of the nature of a true immunization or desensitization but rather one of accentuated or cumulative tuberculin toxicity in the hypersensitive animals. The phagocytic blood cells from specifically immune, allergically tuberculin hypersensitive, anaphylactically hypersensitive or tuberculous guinea pigs phagocytize viable human tubercle bacilli equally well as do the phagocytic cells obtained from normal guinea pigs. The bone marrow cells from allergically tuberculin hypersensitive, anaphylactically tuberculin hypersensitive or tuberculous guinea pigs, whether from animals untreated or treated with tuberculin or heat-killed tubercle bacilli, revealed no appreciable difference as a result of contact with tuberculin when determined by the stained dead-cell technique.

In elaboration of the previous attempts to transfer specific tuberculo-immunity and specific tuberculin allergy in 1945 (13), it was reported that specific tuberculosis immunity produced by means of the injection of viable avirulent tubercle bacilli is not transferred perceptibly to normal recipient guinea pigs by the injection of citrated whole blood from the donors one month and two months after vaccination, when the specific immunity is well developed. Likewise,

specific allergic hypersensitiveness to tuberculin is not transferred by means of the intravenous injection of citrated whole blood from the allergic hypersensitive donors to normal recipient guinea pigs.

However, in spite of all these negative attempts to transfer the tuberculo-(tuberculin) allergic hypersensitiveness, Chase (14) records successful transfer of cutaneous hypersensitivity to tuberculin using the method previously found successful by Landsteiner and Chase (15) for simple compounds (picryl chloride) by using conjugates and obtaining peritoneal exudates with killed tubercle bacilli, the entire procedure being rather involved and susceptible of varied interpretation. Definite results were obtained with acylchloride, O-chlorobenzoyl chloride and citraconic anhydride; and the scratch test was used. The cutaneous sensitivity to tuberculin was produced by exudate cells from guinea pigs sensitized by giving killed tubercle bacilli in paraffin oil and vaseline. The exudate cells were obtained after injecting 28 cc. of paraffin oil intraperitoneally and the washings made with heparinized Tyrode solution containing gelatin or normal guinea pig serum. The tests were performed with OT in some form or at times with the large molecular variety of tuberculin; and these were employed in the highest concentration that produced no reactions, or only trivial ones, in the untreated control animals (a poor basis from which to begin because of the close approximation of nonspecificity to specificity in this range). In addition, the tuberculin tests in these relatively large amounts were repeated, and after the fifth day the controls began to exhibit an active sensitization to the broth control medium. In addition to exudate cells from the peritoneal cavity, cells from the spleen or lymph nodes were found capable of transferring hypersensitiveness to Old Tuberculin. The brief duration of sensitivity and the activity of cells from peritoneal exudates, spleen and lymph nodes are claimed to parallel the experiences in the transfer of drug allergy.

It was not the purpose of the following study to pursue further the attempt to transfer tuberculo-(tuberculin) allergic hypersensitiveness passively. Rather, we wished to obtain further evidence as to whether any local phenomenon could be produced by various ways to suggest that such possibilities existed, and whether it might be possible to utilize such information for practical purposes to discern the presence of tuberculo-(tuberculin) allergic hypersensitiveness in the human being which could obviate immediate or direct test on the individual himself such as is performed with the present tuberculin tests. It now appears to have been established sufficiently, from extensive experimental tests performed by us, that a pure tuberculin (tuberculoprotein) or an autolytic tuberculin given in large amounts to animals will not induce tuberculo-allergic hypersensitiveness to tuberculin when using reasonable specific test amounts and by performing a proper type of test for this purpose to avoid the occurrence of nonspecific borderline reactions.

In the first experiment, a group of 6 normal guinea pigs was used as controls and a similar group of 6 tuberculo-allergic guinea pigs was made allergically hypersensitive to tuberculin by the Saenz method (16) of injecting subcutaneously 1 mg. of heat-killed human tubercle bacilli suspended in 0.1 cc. of min-

*A comparison of the intracutaneous tuberculin reaction with and without blood from tuberculin (allergic) hypersensitive guinea pigs in tuberculo- (tuberculin) allergic hypersensitive animals*

SUBSTANCE USED FOR INTRACUTANEOUS TEST	GUINEA PIGS USED									
	Experiment 1					Experiment 2				
	Normal		Hypersensitiveness produced by heat-killed tubercle bacilli in oil one month prior			Normal		Hypersensitiveness produced by avirulent tubercle bacilli one month prior		
	Tuber- culin reaction	Other reactions	Tuberculin reaction	Other reactions	Tuber- culin reaction	Other reactions	Tuberculin reaction	Other reactions	Tuber- culin reaction	Other reactions
0.001 mg. tuberculin (tuberculo- protein)	0	None	0.8 to 1.5 cm.	None	0	None	0	None	0	None
Citrated normal whole blood (guinea pig)	0	0.8 to 1.5 cm. reddish- brown blood discolora- tion	0	1.2 cm. red- dish - brown blood dis- coloration	0	1.0 to 1.2 cm. bluish - red blood dis- coloration	0	1.0 to 1.2 cm. bluish - red blood dis- coloration	1.0 to 2 cm.	None
Citrated normal whole blood (guinea pig) + 0.001 mg. tuberculin	0	0.8 to 1.5 cm. reddish- brown blood discoloration	0.8 to 1.4 cm.	Purple-red blood dis- coloration	0	1.0 to 1.2 cm. bluish - red blood dis- coloration	1.2 to 1.8 cm.	Pale bluish- red blood discolora- tion	1.0 to 1.4 cm. bluish - red blood dis- coloration	1.0 to 1.4 cm. bluish - red blood dis- coloration
Citrated whole blood from al- lergic hypersensitive guinea pigs (heat-killed bacilli in oil in exp. 1 and viable avirulent bacilli in exp. 2)	0	0.8 to 1.5 cm. reddish- brown blood discolora- tion	0	1.0 to 1.2 cm. red - brown blood dis- coloration	0	1.0 to 1.2 cm. bluish - red blood dis- coloration	0	1.0 to 1.2 cm. bluish - red blood dis- coloration	1.3 to 1.8 cm.	Pale bluish- red blood discolora- tion
Citrated whole blood from al- lergic hypersensitive guinea pigs (as above) + 0.001 mg. tuberculin	0	0.8 to 1.5 cm. reddish- brown blood discolora- tion	1.0 to 1.5 cm.	Purple-red blood dis- coloration	0	1.0 to 1.2 cm. bluish - red blood dis- coloration	1.3 to 1.8 cm.	Pale bluish- red blood discolora- tion	1.0 to 1.4 cm. bluish - red blood dis- coloration	1.0 to 1.4 cm. bluish - red blood dis- coloration

eral oil one month prior to the intracutaneous tests which were then given to both sets of animals. After careful shaving and cleansing of the abdomen, each guinea pig was given the following five intracutaneous injections at five different sites: *site 1*: 0.001 mg. of tuberculo-protein in 0.1 cc. solution as allergic (tuberculin) hypersensitive test; *site 2*: 0.1 cc. of citrated whole blood from guinea pigs allergically hypersensitive to tuberculin (donors sensitized by the injection of heat-killed bacilli in oil one month prior to obtaining the blood); *site 3*: 0.1 cc. of citrated whole blood from guinea pigs allergically hypersensitive to tuberculin (donors sensitized with heat-killed bacilli in oil to which was added the same amount of tuberculin (0.001 mg.) in 0.1 cc. as given in *site 1*); *site 4*: 0.1 cc. citrated blood from a normal guinea pig; and *site 5*: 0.1 cc. citrated normal blood to which was added an equivalent amount of tuberculin (0.001 mg.) as injected into *site 1*. Readings at the intracutaneous site of injection were made at twenty-four, forty-eight and seventy-two hours after the injection with the results recorded in table 1 in which the average readings for the guinea pigs are recorded as illustrative of the findings. In the table the findings of experiment 2 are also included. These were obtained by comparing in identical fashion in another experiment the intracutaneous sites in normal control animals and like sites in tuberculo-allergic hypersensitive animals. Such tuberculo-allergic hypersensitiveness was produced by giving a subcutaneous injection of 1 mg. of viable avirulent human tubercle bacilli one month prior to the test, using for local intracutaneous injection the citrated blood of tuberculo-allergic hypersensitive guinea pigs also prepared by giving 1 mg. of viable avirulent human tubercle bacilli one month prior to obtaining the blood for the test (this to replace the blood from the heat-killed bacilli in oil sensitized pigs of experiment 1); otherwise all procedures were the same in experiments 1 and 2.

The findings recorded in table 1 tend to support the contention that, regardless of whether citrated whole blood from a normal or a tuberculo-allergic (tuberculin) hypersensitive guinea pig is mixed with the tuberculin (tuberculo-protein) used intracutaneously for testing the local hypersensitiveness, it does not markedly accentuate nor depress the tuberculin reaction naturally produced when the same amount of tuberculin is given intracutaneously alone to a tuberculo-(tuberculin) allergic hypersensitive guinea pig in which hypersensitiveness was produced either by the injection of heat-killed tubercle bacilli in mineral oil or by the injection of viable avirulent human tubercle bacilli. The natural color sequence of reactions was noted following the intracutaneous injection of citrated whole blood regardless of whether this was obtained from normal guinea pigs or from tuberculo-(tuberculin) allergic hypersensitive guinea pigs. The blood alone showed no tendency to produce reactions intracutaneously other than that produced by normal citrated blood whether from tuberculo-allergic guinea pigs or not, or whether mixed with tuberculin or not, and given to normal guinea pigs. Such reactions as occurred were predominantly due to the tuberculin (tuberculo-protein) and consisted of the production of acute erythematous edematous inflammatory reactions with tendency to necrosis in the case of violent reactions. However, when citrated blood was mixed with the tuberculin producing a reac-



tion, there tended to occur a masking of the normal blood color reactions as a result of the masking effect of the more prominent inflammatory tuberculin reaction.

#### SUMMARY

1. No evidence was obtained to indicate that a mixture of citrated whole blood from normal or tuberculo-(tuberculin) allergic hypersensitive guinea pigs, with or without tuberculin, tended to produce a reaction when injected intracutaneously into normal or tuberculo-(tuberculin) allergic hypersensitive guinea pigs other than that normally produced by blood or tuberculin alone in these same guinea pigs.

2. Even though *in vitro* evidence from *in vitro* phagocytosis experiments and tissue culture studies indicated the existence of the toxic effect of tuberculin on phagocytic blood cells, there does not appear to be any evidence that tuberculin mixed with citrated blood from tuberculo-allergic hypersensitive (to tuberculin) guinea pigs produces a toxic substance for normal guinea pigs. Nor is there evidence that it retards or accentuates the natural tuberculin reaction in tuberculo-allergic hypersensitive guinea pigs to a sufficient extent to be of practical value for determining the existence of the tuberculo-allergic hypersensitive condition from the blood.

#### SUMARIO

1. No se obtuvieron datos indicativos de que una mezcla de sangre íntegra citratada de cobayos normales o hipersensibles tubérculo-(tuberculina) alérgicos, con o sin tuberculina, fomentara, al ser inyectada intracutáneamente en cobayos normales o hipersensibles tubérculo-(tuberculina) alérgicos, una reacción distinta de la producida en los mismos cobayos normalmente por la inyección de sangre o tuberculina solas.

2. Aunque los datos obtenidos en experimentos sobre la fagocitosis *in vitro* y los estudios de cultivos histológicos indicaban un efecto tóxico de la tuberculina sobre los fagocitos de la sangre, no parece que haya la menor prueba de que la tuberculina mezclada con sangre citratada de cobayos tubérculo-alérgicos hipersensibles (a la tuberculina) produzca una sustancia tóxica para los cobayos normales. Tampoco hay pruebas de que retarde o acentúe la reacción natural a la tuberculina en los cobayos hipersensibles tubérculo-alérgicos, en grado suficiente para que resulte de valor práctico para determinar la existencia del estado hipersensible tubérculo-alérgico derivado de la sangre.

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# SPECIFIC CYTOTOXIC ACTION OF TUBERCULIN

## Studies on Tissues of Tuberculous Rabbits in Which Negative Cutaneous Reactions to Tuberculin Have Developed

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The demonstration of the specific cytotoxic action of tuberculin in tissue culture by Rich and Lewis (1) provided a new approach to the study of bacterial hypersensitivity. Limited use has been made of the technique but other investigators have confirmed the work of Rich and Lewis and have added to the knowledge concerning the cellular aspects of hypersensitivity of the tuberculin type.

There is general agreement that the specific cytotoxic effect is limited to the tuberculin type of sensitivity and is not present in anaphylactic states. A summary of work that has been done with the tissues of tuberculin sensitive animals has been presented elsewhere (2).

The purpose of the present study was to determine whether or not the loss of cutaneous hypersensitivity to tuberculin that sometimes occurs spontaneously in tuberculous animals is also accompanied by a loss or diminution of cellular hypersensitivity.

### MATERIALS AND METHODS

*Animals:* Two groups of adult male rabbits were used in this study. Group 1 consisted of 5 rabbits in the terminal stages of progressive experimental tuberculosis when the loss of cutaneous hypersensitivity to tuberculin occurred. In one instance cultures of material from 2 of the test animals were made on the same day, in an experiment in which only one control rabbit was used. Cultures of material from the 3 remaining rabbits in group 1 were made at different times. As a result, 4 control rabbits were used in this series of experiments. A virulent strain of *Mycobacterium tuberculosis* of the bovine type (Feldman 3724) was used to produce experimental tuberculosis in the test animals. Each rabbit was given an intravenous inoculation of 0.001 mg. of tubercle bacilli grown for thirty days on Proskauer-Beck's synthetic liquid medium. Intracutaneous tests with 1 mg. of Old Tuberculin were performed twenty-eight days after inoculation in order to establish the fact that hypersensitivity to tuberculin had developed in the test animals. Because of the rapid progress of the tuberculous process, frequent intracutaneous tests with 10 mg. of Old Tuberculin were performed.<sup>3</sup> Rabbits in which negative reactions occurred were chosen for tissue culture studies. A negative reaction was one in which induration of the skin was absent and an area of redness at the site of injection was absent or was less than 0.5 cm. in diameter.

The same sample of tuberculin was used for intracutaneous testing and for

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<sup>3</sup> The tuberculin was injected intracutaneously in the region of the back.

the tissue culture experiments. It was preservative-free mammalian tuberculin of Old Tuberculin strength obtained through the courtesy of Dr. H. W. Schoening, Bureau of Animal Industry of the United States Department of Agriculture. The sample used was designated as sample B in previous studies (2 to 4.) Numerous tests with normal rabbits revealed that the intracutaneous injection of 10 mg. of this tuberculin did not cause redness or thickening of the skin forty-eight hours after injection.

Group 2 was composed of 4 rabbits in which a mild form of tuberculosis existed. Failure to react to the intracutaneous tuberculin test was associated with intercurrent infections in these rabbits. Four rabbits were used as controls. A strain of *Mycobacterium tuberculosis* of the human type (Feldman H439) was used to produce a mild form of tuberculosis in the rabbits in this group. The method used and the characteristics of the resulting infection have been described previously (2). Tuberculin tests with 1 mg. of Old Tuberculin were performed during the fourth or fifth week after inoculation. Most of the rabbits in this group were maintained for several months, and those showing loss of weight accompanied by signs of respiratory or intestinal infections were again tuberculin tested. For this purpose a dose of 10 mg. of Old Tuberculin was used. Rabbits showing a negative reaction to tuberculin were selected for tissue culture studies.

*Tissue culture methods:* The quantitative tissue culture technique used in this study has been described in detail elsewhere (2). Blood used in the preparation of tissue culture medium was obtained from normal rabbits exclusively. A portion of the blood was used to prepare heparinized plasma and serum was prepared from the remainder of the blood for use in making serum extract of chick embryos. Serum-chick-embryo extract was made by extracting chick embryos of eight days of incubation with normal rabbit's serum in the proportion of one embryo to 5 cc. of serum. Before the cultures were made a concentration of 1:50 of Old Tuberculin in Tyrode's solution was added to half of the serum-chick-embryo extract to comprise a twentieth of the volume of the medium used in culture preparations. This resulted in a final concentration of 1:1,000 of Old Tuberculin. A similar volume of Tyrode's solution without tuberculin was added to the remaining tissue extract.

Cultures were placed in D-5 Carrel flasks. Each preparation consisted of 0.5 cc. of rabbit's plasma, 1.0 cc. of serum-chick-embryo extract and four explants of spleen which were placed in the medium before clotting occurred. Three flasks, or a total of twelve splenic fragments, were used for each experimental condition. Explants of the spleen of a normal rabbit and of that of a tuberculous rabbit were cultured on the same day in medium containing tuberculin as well as in normal medium. Thus a typical experiment consisted of the following groups of cultures: (1) normal rabbit's spleen in normal medium, (2) normal rabbit's spleen in medium containing tuberculin, (3) tuberculous rabbit's spleen in normal medium and (4) tuberculous rabbit's spleen in medium containing tuberculin.

Cultures were incubated at 37°C. for four days. At the end of this period

measurements of the extent of migration of large wandering cells were made by the use of an ocular micrometer according to the method previously described (2). The relative extent of migration of macrophages from the spleens of tuberculous rabbits in the presence and absence of tuberculin was compared with the migration of macrophages from the spleens of normal rabbits under similar conditions. The results were expressed in terms of a comparative cytotoxic index according to the formula:

$$\text{Comparative cytotoxic index} = \frac{\text{Av. migration (N)}}{\text{Av. migration (N + OT)}} \times \frac{\text{Av. migration (S + OT)}}{\text{Av. migration (S)}}$$

in which N represents cells from normal tissue and S represents cells from tissue of tuberculous animals. A value less than 1 indicates that tuberculin has a specific cytotoxic effect on cells from the tuberculous animal.

### RESULTS

All rabbits inoculated with the strain of *Mycobacterium tuberculosis* of the bovine type (group 1), when tested twenty-eight days after inoculation, gave a positive reaction to tuberculin. These rabbits lost weight rapidly and became negative to a skin test, in which an injection of 10 mg. of tuberculin was made, between forty-nine and sixty-six days after they were inoculated with tubercle bacilli. Most of the test animals were moribund when they were killed. At this time specimens were taken for tissue culture studies. Postmortem examination at this time revealed similar pathological findings in all of the tuberculous rabbits in group 1. The spleens were much enlarged and were filled with small tubercles. Many tubercles were present in the lungs and a few were found in the liver and kidneys.

Explants of the spleen of tuberculous rabbits in group 1 consisted chiefly of tubercles with occasional small remnants of splenic pulp attached. Cultures of the tubercles reacted in a different manner from cultures of normal spleen or the spleen of rabbits with mild tuberculosis produced with *Mycobacterium tuberculosis*, strain H439. The spleens of tuberculous rabbits in group 2 contained few tubercles and the explants selected for tissue culture consisted almost entirely of splenic pulp. In cultures consisting chiefly of tubercles from the spleens of rabbits inoculated with strain 3724 an initial migration of small wandering cells or leucocytes, such as appears in cultures of normal spleen, was not observed. Instead there was a prompt migration of medium and large-sized wandering cells, which formed a dense zone of migration around the explants within a few hours. A few small cells migrated at the same time, but they were obscured and were soon removed from the migration zone by the macrophages. The area of cellular extension became wider during the second and third days of incubation. At ninety-six hours the migration zones were approximately as wide as those seen in cultures of spleen from tuberculous rabbits in group 2. There was a distinct difference, however, in the appearance of the two groups of cultures. The individual macrophages present in both instances were similar in appearance but they were much more numerous in cultures from group 1 that consisted chiefly of

tubercles than they were in cultures of splenic tissue of rabbits with mild tuberculosis (group 2).

The results of tissue culture studies of the tuberculous rabbits in group 1 are presented in table 1. The radius of migration of macrophages from tissue removed from the test animals was significantly decreased in every instance in cultures containing tuberculin. In one experiment in this series tuberculin caused an increase, and, in another experiment, a decrease in the migration of normal macrophages. The relative sensitivity of macrophages derived from cultures of tubercles compared with normal cells was about the same as that of macrophages from the splenic pulp of rabbits with mild tuberculosis.

Three of the 4 tuberculous rabbits in group 2 gave a positive reaction to the first intracutaneous tuberculin test. The remaining rabbit (table 2; experiment

TABLE 1

*Effect of Old Tuberculin on migration of macrophages from spleens of rabbits in group 1*

EXPERIMENT NUMBER	NORMAL CULTURES		TEST CULTURES		COMPARATIVE CYTOTOXIC INDEX	DURATION OF INFECTION
	Normal medium	Medium with OT	Normal medium	Medium with OT		
	Radius of migration*	Radius of migration	Radius of migration	Radius of migration		
1	229 $\pm$ 26	256 $\pm$ 9	575 $\pm$ 4	237 $\pm$ 12	0.37	days 49
2	217 $\pm$ 5	202 $\pm$ 9	542 $\pm$ 18	245 $\pm$ 7	0.49	53
			515 $\pm$ 6	242 $\pm$ 5	0.50	53
3	310 $\pm$ 11	252 $\pm$ 13†	575 $\pm$ 20	386 $\pm$ 11	0.83	54
4	223 $\pm$ 6	264 $\pm$ 7‡	688 $\pm$ 14	457 $\pm$ 14	0.56	66

\* The value following the  $\pm$  is the standard error of the mean.

† Significant decrease in migration.

‡ Significant increase in migration.

1) reacted negatively and at the same time was emaciated and had a purulent nasal discharge and diarrhea. At the time tissue was removed for cytotoxicity studies it was found that the spleen of this rabbit was much enlarged, and the lungs showed regions of gray consolidation in both upper lobes. Several months after inoculation with tubercle bacilli respiratory infections developed in the 3 rabbits that gave a positive reaction to the intracutaneous tuberculin test. When the tuberculin reactions became negative in these rabbits, they were used for tissue culture studies. At necropsy regions of gray consolidation in the upper lobes of both lungs were evident in all 3 rabbits. The tuberculous rabbit used in the second experiment in group 2 had a few tubercles scattered throughout the lungs but none were found in the liver, kidneys or spleen. Tubercles were not seen grossly in the tissues of the rabbits used in experiments 3 and 4, but

colonies of acid-fast bacteria resembling *Mycobacterium tuberculosis* grew on egg-yolk-glycerin-agar cultures of tissue from the lungs of both rabbits. The results of tissue culture studies in group 2 are presented in table 2. The concentration of tuberculin used did not cause a significant change in the rate of migration of normal macrophages. A significant inhibition of migration of macrophages from the test animals in cultures containing tuberculin was noted in all four experiments. However, in one instance (experiment 2) the inhibition observed was not greater than that occasionally present in cultures of normal tissue containing the same concentration of sample B of Old Tuberculin (table 1, experiment 3). In the three remaining experiments in this group the results were similar to those obtained in previous studies of rabbits inoculated with *Mycobacterium tuberculosis* strain H439 that had a positive skin reaction to tuberculin.

TABLE 2

*Effect of Old Tuberculin on migration of macrophages from spleens of rabbits in group 2*

EXPERIMENT NUMBER	NORMAL CULTURES		TEST CULTURES		COMPARATIVE CYTOTOXIC INDEX	DURATION OF INFECTION
	Normal medium	Medium with OT	Normal medium	Medium with OT		
	Radius of migration*	Radius of migration	Radius of migration	Radius of migration		
						months
1	301 $\pm$ 16†	257 $\pm$ 16	414 $\pm$ 14	162 $\pm$ 4	0.46	1
2	444 $\pm$ 9	421 $\pm$ 11	718 $\pm$ 15	615 $\pm$ 22	0.90	7
3	419 $\pm$ 9	389 $\pm$ 11	596 $\pm$ 23	348 $\pm$ 9	0.63	10
4	187 $\pm$ 6	188 $\pm$ 6	283 $\pm$ 7	139 $\pm$ 4	0.49	15

\* The value following the  $\pm$  is the standard error of the mean.

† The control rabbit in this experiment was suffering from a respiratory infection and was extremely emaciated.

#### COMMENT

The results of the present study affirm the view generally held at the present time that a spontaneous loss of cutaneous sensitivity to tuberculin does not necessarily indicate a loss or diminution of systemic hypersensitivity. Kraus, Löwenstein and Volk (5) observed that guinea pigs in the last stages of tuberculosis that gave a negative reaction to the intracutaneous tuberculin test also failed to react to the intracutaneous injection of diphtheria toxin. Pilcher (6) reported that persons who had tuberculosis and who gave negative reactions to the intracutaneous tuberculin test during intercurrent infections or in the terminal stages of tuberculosis also lost the ability to react to the intracutaneous injection of a nonspecific irritant (codeine). All of the rabbits used in the present study had lost weight, and the failure of the skin to react to tuberculin in tuberculous animals in groups 1 and 2 may have been due to an impairment of capillary circulation accompanying cachexia. At any rate, failure of the skin to react to tuberculin was not accompanied by detectable changes in the migratory activity of the cells or their sensitivity to tuberculin in the majority of experiments. In one test the results obtained were equivocal.

It would have been desirable to use the tissue culture method to study two other conditions in which there is loss of cutaneous hypersensitivity to tuberculin; namely, in healed or arrested tuberculosis and during desensitization of tuberculous animals with tuberculin. To study these conditions would have required further long periods of observation and facilities that were not available when the present studies were made.

Freund (7) has shown that young guinea pigs infected with the mammalian type of tubercle bacilli gave a negative reaction to the intracutaneous tuberculin test but were sensitive to the lethal action of tuberculin injected into the peritoneal cavity. Aronson (8) stated that cultures of spleen and bone marrow of very young tuberculous guinea pigs were as sensitive to tuberculin as cultures of similar tissue from adult guinea pigs with tuberculosis. The results obtained by Aronson and those of the present study suggest that the specific cytotoxic reaction may be a more reliable index of the state of tuberculin hypersensitivity than the intracutaneous test. By using the leucocyte layer of centrifuged blood as a source of cells it is possible to determine the specific cytotoxic reaction without killing the test animals (1, 2).

#### SUMMARY AND CONCLUSIONS

A tissue culture method was used to study the specific cytotoxic action of tuberculin on tissues from tuberculous rabbits in which negative cutaneous reactions to tuberculin had developed. The results of tests done with 5 rabbits in the terminal stages of progressive experimental tuberculosis indicated that a definite cellular sensitivity to tuberculin was present in each instance. Four experiments were done with tissue from rabbits with mild experimental tuberculosis which had become skin-test negative to tuberculin while they were suffering from intercurrent infections. In 3 experiments of this series a definite cellular hypersensitivity to tuberculin was observed, and in one experiment the results obtained were ambiguous.

It is concluded that a so-called spontaneous loss of cutaneous hypersensitivity to tuberculin in the course of experimental tuberculosis was not accompanied by a decrease or loss of cellular hypersensitivity.

#### SUMARIO Y CONCLUSIONES

Empleóse una técnica de cultivo histológico para el estudio de la acción citotóxica de la tuberculina sobre los tejidos de conejos tuberculosos en los cuales se habían obtenido cutirreacciones negativas a la tuberculina. Los resultados de las pruebas en cinco conejos en las etapas terminales de la tuberculosis experimental evolutiva indicaron, en todos, una sensibilidad celular bien definida a la tuberculina. Se realizaron cuatro experimentos con tejidos de conejos con tuberculosis experimental leve que se habían vuelto dermonegativos a la tuberculina mientras los animales sufrían de infecciones concomitantes. En tres experimentos de esta serie se observó hipersensibilidad celular a la tuberculina y en un experimento los resultados obtenidos fueron ambiguos.

Se saca en conclusión que la llamada pérdida espontánea de la hipersensibilidad



cutánea a la tuberculina en el curso de la tuberculosis experimental, no se acompañó de disminución o pérdida de la hipersensibilidad celular.

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## EDITORIAL

### Tuberculosis in a Screened Population

According to a tentative report the combined tuberculosis mortality rate in 1945 for present and past members of the Army of the United States who have served with the Army since December 8, 1941 was approximately 12 per hundred thousand. This is a substantial increase over the reported mortality rate of 3 per hundred thousand in 1942,<sup>1</sup> and gives an indication of the extent and rapidity with which tuberculosis may develop in a screened population. That the increase is gradual but progressive is shown by charts recently exhibited,<sup>2</sup> which show a mortality of 3 per hundred thousand in 1942, 6 in 1943, 10 in 1944 and 12 in 1945.

Data are not yet at hand for determination of the full significance of these figures. Prolonged and intensive research will be required to learn how much of the infection responsible for the mortality was brought into the Army in undetected form or at least unsuspected severity at the time of induction, and how much was introduced after acceptance for military service. Previous reports<sup>3</sup> have indicated that approximately one million men, out of the total of eleven million who had Army service, were inducted without X-ray examination. A few thousand men with pulmonary tuberculosis were presumably taken in with this group. Attention has been called from time to time also to the imperfections of X-ray examination in the induction stations which resulted in the acceptance of an appreciable number of men with minimal disease either already active or supposedly arrested, but actually, as proved subsequently, not arrested. The number of soldiers in this category has been roughly estimated as about 10 per cent of those rejected for active or potentially active tuberculosis, and the reasons for failure of detection were given in some detail at the last meeting of the National Tuberculosis Association.<sup>4</sup> It may be assumed without question that a substantial proportion of the mortality from tuberculosis occurred in the group of men who were thus unwittingly admitted to the Army with significant tuberculous lesions.

On the other hand, it is well known that numerous cases of tuberculosis, particularly in the late years of the war, developed in men whose induction films failed, on recheck, to reveal any evidence of infiltration. The advent of clinical tuberculosis in these men must be looked upon as either development from hidden foci not evident in X-ray films or from fresh infection from without.

It is to be hoped that facilities will ultimately be afforded permitting a careful review of induction and separation films, and enabling a better index than is

<sup>1</sup> Am. Rev. Tuberc., 1945, 51, 489.

<sup>2</sup> Scientific Exhibit, American Medical Association, San Francisco, California, July 1 to 5, 1946.

<sup>3</sup> Am. J. Pub. Health, 1945, 35, 469.

<sup>4</sup> LONG, ESMOND R.: A résumé of the tuberculosis experience of the United States Army in World War II, to be published in Am. Rev. Tuberc.

at present available of the extent to which tuberculous infection from without occurred in the Army during the war years. Pending that investigation, however, the mortality figures now at hand will prove of great interest, both practical and theoretical. They furnish an indication of the speed at which mortality rises in a screened population—screened with the imperfections noted, which have their counterpart in all surveys—and at the same time they are of great theoretical interest in comparison with the tuberculosis mortality for the civilian male population of corresponding age. During the four-year period, in which the mortality of the screened group rose from 3 to 12 per hundred thousand per year, the gross mortality rate for the comparable unscreened civilian population remained, with minor fluctuations, at approximately 52. Presumably no one would care to hazard an estimate as to how high the rate in the screened population will go. It might conceivably increase until it equals that of the unscreened civilian population of corresponding age, which, itself, may be expected to decrease with the passage of time and improvement in effectiveness of general antituberculosis measures. On the other hand, certain retarding influences, such as the case-finding measures incorporated in the out-patient program of the Veterans Administration, may halt the upward climb now evident and stabilize it on a grade well below that of the population at large. Time will furnish the answer, for the required data will become available through the vital statistics of the Veterans Administration.

ESMOND R. LONG

## Fred Henry Heise

1883-1946

The many friends and former patients of Doctor Heise will be saddened to hear of his death at the early age of 63. His illness was fortunately short as it was recognized as an incurable carcinoma from the first. Trudeau Sanatorium has lost a leader and a beloved physician whose long service will be remembered for its rare conscientiousness.



Fred Henry Heise

1883-1946

His modesty and shyness concealed his true worth, so that public recognition came relatively late in life. Nevertheless his patients in the Sanatorium had always trusted him implicitly and appreciated the good judgment and advice that he gave.

Like many other young physicians who have sought treatment at Trudeau Sanatorium, he developed tuberculosis within a year after graduating in medicine. He received his preliminary education in the Baltimore city schools and City College, and he took his degree in medicine at the University of Maryland in 1907. While never of vigorous constitution he nevertheless made a good recovery under the care of the late Lawrason Brown, who recognized his valuable qualities and encouraged him to take up the study of tuberculosis. Among the many physicians who were trained under Doctor Brown, Fred Heise proved so exceptionally promising that he was soon appointed an Assistant Physician. After two years of service, during which he helped to systematize the methods of treatment which Doctor Brown had inaugurated, he left Trudeau in 1911 to take a position as resident physician in the Maryland State Sanatorium with Dr. Victor F. Cullen. Remaining there only one year, he returned to Trudeau as its first Resident Physician and in 1929, on the retirement of Doctor Brown, succeeded him as Medical Director.

During his thirty-four years of faithful service, Doctor Heise witnessed a truly phenomenal decrease in the incidence of tuberculosis. Through his experience and studies he contributed much of practical value in the prevention and treatment of the disease. As a lecturer in his field, his services were in constant demand, and besides many contributions to current literature he published in association with Doctor Brown, in 1931, a popular work on *The Lungs and the Early Stages of Tuberculosis*, suited not only for intelligent patients but also for physicians. His answers to patients' questions, which first appeared in successive numbers of the *Journal of the Outdoor Life*, will long be remembered. In 1935 he collected and published the most significant ones under the title *1000 Questions and Answers on T. B.* This little volume has run through several editions and still constitutes an authoritative source of information for patients.

As these publications testify, Doctor Heise was a constant student of the clinical aspects of pulmonary disease. He was thoroughly familiar with the literature and initiated much of the scientific and experimental work which was in progress in the laboratories.

Doctor Heise was a member of the local, state and national medical societies, notably the National Tuberculosis Association, of which he was President in 1944-1945 and Chairman of its Diagnostic Standards Committee for twelve years. He was President of the American Sanatorium Association and President of the Eastern Section in 1931-1932; a member of the American Trudeau Society and of the American Climatological and Clinical Association; a lecturer in the Trudeau School of Tuberculosis and lecturer (non-resident) on tuberculosis in the University of Rochester School of Medicine.

He was Chairman of the Medical Board of Trudeau Sanatorium in 1932-1937 and 1944 until his death on June 8, 1946; a Trustee of Potts Memorial Hospital, and a Director of the Saranac Lake Study and Craft Guild.

He was an active member of the Presbyterian Church of Saranac Lake, and participated in various movements for the benefit of the village.

In 1914 Doctor Heise was married to Miss Ethel Roberts, who was superintendent of nurses at that time. This notice would be incomplete without a tribute to the devotion of Mrs. Heise to her husband and his life's work and to the help and support which she gave him.

His colleagues will always hold Doctor Heise in affectionate memory as a physician who gave his entire life to his professional work.

EDWARD R. BALDWIN

## NOTICE

### Rose Lampert Graf Prize

For the best paper dealing with any aspect of chest, anatomy, physiology, or pathology, or the therapy of chest disease, an award of \$250.00 will be made by the Rose Lampert Graf Foundation. Eligibility is not restricted by nationality or training but the article must be written in English. The prize paper will be read at the 1947 meeting of the American Association for Thoracic Surgery and will be published in the Journal of Thoracic Surgery. The Chairman of the Prize Committee is Dr. Frank B. Berry, Bellevue Hospital, New York City, and papers must be submitted to him before January 15, 1947.

Applicants who wish their papers considered for the program of the American Association for Thoracic Surgery meeting, regardless of the prize award, should send comprehensive abstracts in quadruplicate to the Secretary, Dr. R. H. Meade, Jr., 55 East Washington Street, Chicago, Illinois, before January 15, 1947.

# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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**Eosinophilic Infiltrations in Lung.**—Between 1931 and 1936 Löffler reported 51 cases in which transient pulmonary exudates existed associated with eosinophilia. He considered the condition a well defined clinical entity characterized by pulmonary infiltrations of four types: (1) massive areas of infiltrations simulating tuberculous consolidation, (2) smaller round single foci, (3) multiple small infiltrations in both lungs, (4) lobar involvement simulating abortive pneumonia. All of these were characterized by sudden appearance with complete disappearance in three to eight days. Eosinophil counts were as high as 66 per cent, averaging 10 per cent to 30 per cent. The degree of eosinophilia apparently had no relation to the extent of pulmonary infiltration. Little or no fever, few pulmonary or constitutional symptoms with few physical signs were reported. Other authors have reported cases with more severe symptoms of longer duration. Usually the infiltrations are of homogeneous density and varying size. They may be confluent and patchy in appearance or resemble lobar consolidation. Sometimes they seem to radiate from the hilum with confluent patches in the periphery. In such, complete resolution usually occurs with a few linear strands remaining. Tuberculosis or bronchopneumonia may be suspected, or it may even have some of the appearance of a stage of Boeck's sarcoidosis. Often narrow patch-like densities are seen extending caudad and laterally, and this condition may be bilaterally symmetrical. Most observers believe that the condition is allergic in origin although Löffler stressed the tuberculo-toxins. Leitner believed the infiltrates to be hyperergic

in character and due to different causes, including allergy about tuberculous lesions. Most cases are benign giving little postmortem material. Meyenburg observed the post-mortem findings in 4 grossly different areas of infiltrations resembling focal pneumonias. The microscopic examination in all cases showed extensive eosinophilia in the exudate. In 2 cases there was eosinophilic bronchitis and bronchiolitis. Eosinophilia of blood and bone marrow was present in all cases, while in 2 eosinophilic infiltrations of the liver were found. Harkavy recently described 16 cases, all of whom showed the usual eosinophilia and pulmonary exudates, but also described allergic history in all, pulmonary infiltration of long duration and recurrences. Clinical symptoms are not always mild and many had analogous reactions in other tissues and organs. Pleural and peritoneal exudates showed 85 per cent to 100 per cent eosinophils. X-ray findings may thus be attributed to reactions in lungs and pleura analogous to wheal formation in skin. In this way the scattered and oblique plate-like areas can best be explained.—*Röntgen Features of Eosinophilic Infiltrations in the Lungs*, H. Hennell & M. L. Sussman, *Radiology*, April, 1945, 44: 328.—(G. F. Mitchell)

**Loeffler's Syndrome and Ascaris.**—X-ray films were taken of 221 men in two military units. They ranged in age between 20 and 38. Thirty infiltrates were discovered, of which 2 were tuberculous and the remainder Loeffler's. Of the group of 28, which constituted 12.2 per cent of the total, only 9 had symptoms. The X-ray film showed normal lungs within six to twelve days. Leucocytosis was present in 3



cases, and eosinophilia of over 10 per cent in 13. Skin test with extract of *Ascaris* was positive in 59 per cent of the patients and in 30 to 40 per cent of the controls. In 15 cases ascaris was demonstrated in the stools. It is felt that this endemic infestation with ascaris resulted from the common kitchen, and that the Loeffler's syndrome which resulted was an allergic manifestation.—*Endemisches Auftreten eosinophiler Lungeninfiltrate in einer militärischen Einheit*, O. Spühler & M. Kartagener, *Schweiz. med. Wchnschr.*, November 4, 1944, 74: 1145.—(J. Gerstein)

**Loeffler's Syndrome and Ascaris.**—Loeffler described the clinical picture of transient pulmonary infiltration and eosinophilia in 1932. The disease is benign, lasting eight to ten days, with slight fatigue, temperature that is normal or only slightly elevated and dry cough. Occasionally there is a clear yellow sputum with numerous eosinophils. Physical findings are few, and consist of diminution of breath sounds, crepitant râles and, rarely, a friction rub or signs of fluid. X-ray film shows a soft, flaky opacity, present on one or both sides, without definite margins unless resting on a fissure. The lesion is rarely present in an apex. The radiographic findings last three to seven days. The blood findings last two to three weeks, longer than any other abnormality. There are mild leucocytosis and lymphopenia, with eosinophilia from 7 to 85 per cent, usually between 10 to 20 per cent. Autopsy which is rare, shows a pneumonia or bronchopneumonia, with little fibrin, many eosinophils, giant cells and many small alveolar hemorrhages. Mild atypical bronchopneumonia, epituberculosis, and allergy to cold or pollens have been given as etiological factors. Müller, in 1938, and Vogel and Minning, in 1942, reproduced the symptoms of Loeffler's syndrome by swallowing ascaris eggs. They also showed that the eggs are not found in the stool for ten weeks, but may be demonstrated in five to seven weeks if an anthelmintic is given. Careful examination of the sputum reveals ascaris and giant cells. This shows that the pulmonary response is not allergic,

but caused by the presence of the worm. The exact path from the intestines to the lungs is not known. It is felt that infestation with ascaris is the most common cause of Loeffler's syndrome.—*A propos de l'infiltrat pulmonaire fugace avec éosinophilie sanguine et de son étiologie le plus souvent vermineuse*, F. Cardis, *Schweiz. med. Wchnschr.*, February 24, 1945, 75: 165.—(J. Gerstein)

**Pulmonary Acariasis.**—In view of the attention recently directed to the possible significance of mites in the causation of certain pulmonary disorders such as asthma, bronchitis and "eosinophil lung," the author thought it of interest to describe an autopsy performed on a *Macacus* monkey in 1933. Small nodules were noted scattered through the lungs. On teasing out some of the nodules minute arthropods were found—they were identified as mites belonging to the genus *Pncumonyssus*. Microscopically the nodules consist of capsules, the walls of which are composed of cellular granulation tissue. The lumen of each capsule is lined by epithelial cells and usually contains an arthropod lying among cellular detritus. The tissue comprising the walls of the capsules consists of fibroblasts, leucocytes, eosinophils, plasma cells and endothelial cells. The nodules are generally in close proximity to bronchioles, but in no instance could direct continuity be detected between a bronchiole and the lumen of a capsule. This demonstration might be held to lend strong support to the concept of pulmonary acariasis in man. However, it is not improbable that these mites may normally exist as ectoparasites on the skin of the host. Nevertheless, if man be exposed to environmental conditions resulting in the aspiration of extraneous mites, it would be reasonable to suppose that, as in monkeys, structural lesions may ensue. That such lesions may give rise to symptoms is quite conceivable.—*Pulmonary Acariasis in Monkeys*, L. I. Davis, *Brit. M. J.*, April 7, 1945, 1: 452.—(D. H. Cohen)

**Tropical Eosinophilia.**—Eosinophilia with pulmonary disease is not a disease entity. It

has been described under many names, and as being secondary to different, widely divergent, etiological causes. Recently it has been seen more frequently in men who were invalided back to England from protracted stays in India. Five cases were observed recently. The illness was characterized by a symptomatology which most often suggested bronchitis, and usually they were so diagnosed originally. Blood eosinophilia varied from 9 to 32 per cent. Two cases showed fairly characteristic X-ray opacities such as have been described, but the other 3 cases had negative chest films. The disease was subject to exacerbation and a decisive therapeutic result was obtained with six injections of neoarsphenamine. No pathogenic parasite was recovered from any of the body secretions and the belief that the syndrome is an allergic manifestation due to a variety of allergens is reiterated.—*Tropical Eosinophilia*, J. Apley & G. H. Grant, *Lancet*, June 30, 1945, 248: 818.—(H. Marcus)

**Sarcoidosis and Tubercle Bacilli.**—Since the advancement of the term *lymphogranuloma benignum* by Schaumann for Boeck's sarcoidosis arguments have been advanced both for and against the assumption of the tuberculous etiology of this disease. Important arguments have been advanced for the tuberculous etiology "by the not so few cases revealing a development of *lymphogranuloma benignum* into a classic caseating tuberculosis." The experimental work of Lemming, Kveim and Kallos has given new and important support to the contention that tuberculosis and *lymphogranuloma benignum* are different phases of the same disease. An additional contribution was made by this author in a case of simultaneous *lymphogranuloma benignum* and tuberculosis of the lungs. A suspension of the patient's own tubercle bacilli was injected intracutaneously and after a month a productive reaction having the histological picture of Boeck's sarcoid was produced at the site of injection, thus leading to the conclusion that Boeck's sarcoid is in reality noncaseating tuberculosis.—*Boeck's Sarcoid, Experimentally Produced by Virulent, Human Tubercle*

*Bacilli in a Case of Schaumann's Disease*, L. E. Warfvinge, *Acta med. Scandinav.*, 1948, 114: 259.—(E. R. Loftus)

**X-ray Therapy of Boeck's Sarcoidosis.**—The cause of sarcoidosis and its relationship to tuberculosis remain in dispute. However, practically every organ or system may be involved and, regardless of location, the histological appearance of the disease is uniform. Because of this appearance, pathologists are prone to classify the disease as hyperplastic or noncaseous tuberculosis. The most frequent sites are probably the mediastinal lymph nodes and pulmonary tissues. Here X-ray is important in the diagnosis as cutaneous or other extensive manifestations as well as clinical signs may be absent. Enlargement of mediastinal lymph nodes is an invariable feature, the pulmonary involvement varying in appearance. Because of the usually benign nature of the process and the tendency to spontaneous recovery over periods of time, it may never be possible to obtain tissues for microscopic study, and the diagnosis must often remain presumptive. Treatment has been empirical and has included many agents and drugs. Roentgen-rays and radium have been successful in treatment of skin lesions, especially in the Darier-Roussy type and also in the Boeck lesion. Evaluation of treatment is difficult because of the tendency to spontaneous recovery. While earlier workers found X-ray of little benefit, later reports of treatment of enlarged lymph nodes and pulmonary disease have been favorable. In order to obtain definite and current opinion, the authors sent questionnaires to 33 radiologists in the United States and Canada. According to the answers, very few patients have received roentgen therapy. Most of the radiologists have no experience with it, and some advised against it. In the past two years 14 patients have been treated by roentgen-ray for chest lesions of Boeck's sarcoidosis at the State of Wisconsin General Hospital. Eight have been observed long enough to warrant preliminary conclusions. Six of the 8 have shown definite X-ray evidence of improvement. Two cases were

followed for twenty-two and twenty-three months before treatment was started and showed consistent progression of disease. Clinical improvement preceded objective evidence of improvement in the 6 cases showing improvement. This was noted two to four months after treatment was started. Of the remaining 2 cases, one showed improvement after five months and one failed to return for follow-up. The method of treatment was six exposures of 150 r to the anterior and posterior mediastinum (15 x 20 cm. port), one area daily, using 175 kv, half-value layer equal to 1.05 cm. Cu. The patient was given a second series in six to eight weeks using same factors. Two patients received a third series after a two-month interval. Other lymph nodes involved usually received 3 x 150 r daily or every other day, repeated once or twice at one to six weeks. Cases are reported in detail. Most of the patients were females and belonged to the middle-age group. Two cases were proved by biopsy. The others were diagnosed by X-ray only. No relationship between the type and the severity of involvement, duration of disease and response to treatment can be established. It is felt that more observation and further studies are necessary to determine the efficacy of the treatment proposed, but radiologists are encouraged to give this treatment a trial.—*Roentgen Therapy of Boeck's Sarcoid*, E. A. Pohle, L. W. Paul & E. A. Clark, *Am. J. M. Sc.*, April, 1945, 209: 503.—(G. F. Mitchell)

**Sarcoidosis.**—A case of Boeck's sarcoidosis is presented with several interesting features: Onset at the age of 10, the disease persisted for thirty-four years. There was no hypertrophy of lymph nodes and the tuberculin skin test was positive. There were hypertension and albuminuria, which possibly were due to a renal localization of the disease. The diagnosis was made on the basis of a histological examination.—*Maladie de Besnier-Boeck-Schaumann, lésions cutanées et pulmonaires d'apparence tuberculeuse*, J. Vidal, H. L. Guibert & M. Girard, *Rev. de la tuberc.*, 1943, No. 4/6, 8: 58.—(G. Simmons)

**Atelectasis in Epistaxis.**—Bronchial obstruction is by far the most important cause of pulmonary atelectasis. Tumors and foreign bodies are the main causes of such obstruction. Blood, as one of the foreign bodies involved, is usually present as a result of hemoptysis. The author describes a case of atelectasis due to epistaxis. The patient was in good health, with no opiates having been used. The epistaxis was due to a drying of the nasal mucosa with crust formation and dilation of the septal vessels. This is believed to be the first case of the kind described in the literature.—*Lungenatelektase bei Epistaxis*, M. Kartagener, *Schweiz. med. Wchnschr.*, January 20, 1945, 75: 62.—(J. Gerstein)

**Spray in Bronchial Asthma.**—Adrenalin spray was first used in asthma in 1910, with further development by Stäubli in 1913. This method did not find wide application until 1942, when Fischer showed that local effects were present on inhalation of fine spray, with droplets below 0.05 cc. in size. Voegtli and Verzár used aleudrin (isopropyladrenalin) in their experiments. In 15 patients with asthma the vital capacity twenty minutes after a two-minute period of inhalation of aleudrin showed an increase of 220 to 1,230 cc. This was an increase of 10 to 50 per cent, an average of 25. The effect lasted three to eight hours. One or two inhalations of this one per cent solution of aleudrin also produced a definite effect, with only 0.06 mg. used, but the effect was of much shorter duration. There was no evidence of any change in the respiratory rate, but there was a slight decrease in the depth of respiration. In 41 healthy students there was no change in the vital capacity under the same conditions. The effect in asthmatics was local, with no apparent general effect.—*Beeinflussung von Vitalkapazität und Atmung durch broncholytisch wirkenden Spray bei Asthma bronchiale und beim Normalen*, W. Voegtli & F. Verzár, *Schweiz. med. Wchnschr.*, May 26, 1945, 75: 457.—(J. Gerstein)

**Emphysema.**—Most clinicians maintain that pulmonary emphysema is an irreparable

disease due to intrapulmonary degenerative changes and that its presence is of secondary importance. Alterations in type of breathing, posture and lung volume are interrelated phenomena that build a pathophysiological triad which, when established in a normal individual, is maintained as a vicious circle leading to emphysema. Changes of breathing type and posture, together with lung volumina, establish the cardinal symptoms of this disorder and manifest themselves as dyspnea, chest pain and cough with a feeling of oppression. This author maintains that normality can be reestablished in the absence of organic disease by a treatment which normalizes the posture and the breathing movements and at the same time the size of the lungs, vital capacity and residual air volume. Essential in the treatment is the correction of posture by medical gymnastics and breathing exercises. The etiological basis of emphysema in most patients involves cough involving affections of the mucous membranes of the air passages, nasal disease with obstruction, cardiac disease or habitual postural anomalies. The author presents a survey of the abnormal types of respiration and of different postural anomalies causing a dilation of the lungs. The question of treatment and prophylaxis is touched upon.—*The Emphysema of the Lungs, Its Symptoms and Relations to Other Diseases*, H. Heckscher, *Acta med. Scandinav.*, March 17, 1945, 120: 349.—(E. R. Loftus)

**Bullous Emphysema.**—The author presents 3 cases of emphysematous bullae of the lungs, one of which terminated fatally. His conclusions are that bullous pulmonary emphysema may appear partly as an attending phenomenon to fibrous lung disease and protracted bronchial valvular stenosis and that another group exists as a primary affection apparently not depending upon preceding or coexisting disease. The degenerated lung tissue acts as a series of valves and their mechanism functions by pressure changes upon them in the course of respiration.—*Emphysema pulmonum bullosum*, P. Owren, *Acta med. Scandinav.*, 1945, 114: 127.—(E. R. Loftus)

**Giant Emphysematous Bleb.**—A 51-year-old cobbler, who suffered from mucopurulent expectoration, dyspnea and pain is reported. The X-ray film showed a cavity occupying the entire upper lobe down to the seventh rib posteriorly. Over this cavity, no physical signs could be heard. As differential diagnoses had to be considered: tuberculosis, bronchiectasis, lung abscess, cyst, emphysematous bleb, hydatid cyst. There was very little sputum, which was negative for acid-fast bacilli and elastic fibres. The patient was treated symptomatically. Three years later he was readmitted with the symptoms of severe alveo-bronchitis and cardiac decompensation. At this time the X-ray film showed that the cavity had completely disappeared. An autopsy was done and a retracted scar was found in the right upper lobe involving the pleura. This is explained as the remainder of a ruptured giant emphysematous bleb which was located subpleurally. Incidentally, numerous small dense nodules were found throughout both lower lung fields which looked in the X-ray like a productive type of tuberculosis. The autopsy showed that this condition was caused by nonabsorbed iodized oil which had been introduced three years previously. The lung had evidently lost its capacity of absorption.—*Enfisema ampolloso gigante simulando una amplia cavidad pulmonar*, I. M. Hernandez, *Arch. argent. de fisiol.*, January-March, 1945, 21: 150.—(W. Swienty)

**Pneumoconiosis.**—Pneumoconiosis can be divided in three principal groups: silicosis and asbestosis, modified silicosis and benign pneumoconiosis. Silicosis and asbestosis produce specific pathological lesions in the lungs. They are due to the inhalation of free silica and of asbestos dust. Modified silicosis is produced by the inhalation of a dust containing a significant amount of free silica combined with a highly concentrated non-siliceous dust. Benign nonspecific pneumoconiosis results from the inhalation of organic or inorganic dusts which are neither toxic, allergenic nor pathogenic. They produce fibrosis but no nodulation. Symptoms

are absent. In the group of benign pneumoconiosis have been included baritosis and siderosis. The former occurs in baryta miners the latter in electric arc welders. Four cases of siderosis are reported which occurred in metal grinders. Silicosis was excluded by eliminating significant exposure to free silica. The grinders were employed in a dry grinding process for a bearings company. The metal ground contained about 98 per cent iron about 2 per cent alloy and not more than 0.2 per cent free silica. The abrasive wheels were composed of bakelite, carborundum and aloxite. It is impossible to differentiate the roentgenological appearance of nodulation of silicosis or the pseudonodulation of benign pneumoconiosis from the shadows cast by many other pulmonary diseases. Detailed knowledge of the occupational history, the environmental conditions and the precise information regarding the nature, concentration and particle size of the dust is necessary in order to differentiate between silicosis and benign pneumoconiosis. Benign pneumoconiosis is not disabling; it produces nothing but shadows cast on a roentgenogram. —*Benign Pneumoconiosis, E. P. Pendergrass & S. S. Leopold, J. A. M. A., March 24, 1945, 127: 701.*—(H. Abeles)

**Silicosis in Sweden.**—The author made a comprehensive study of silicosis in the industries in Sweden. Two thousand, six hundred and thirty-one workers in various industries were examined. The following classification of the material was made on the basis of the International Congress of Johannesburg: first stage: needle-head size foci; second stage: the spot-like foci are larger, the upper limit being pea size; third stage: foci larger than pea size, which fuse and form massive areas. The author made two studies in the porcelain industry (1934 and 1939). Of 1,205 employees examined, there were 614 who worked in dusty occupations. The earliest case of silicosis was observed after ten years of exposure, and the third stage after about thirty-five years. He concludes, by comparative reports, that silicosis in Sweden's porcelain

industry occurs after a long period of exposure and that the disease progresses to the same extent as in other countries. There were 11 cases in which active pulmonary tuberculosis developed. His findings do not substantiate the opinion generally held that there is a high tuberculosis morbidity in porcelain workers. The incidence of silicosis in the employees of iron works was 31.3 per cent. The first stage was seen to develop after ten to fifteen years exposure and the second and third stages after fifteen to twenty years. In foundry workers, the author found that the first stage of silicosis developed in the 41 to 56 year age group, after a twenty to twenty-five year exposure. The silicosis developed so slowly that the advanced forms occur in the age group that is ordinarily ready for retirement. There were 229 cast-iron polishers examined, 81 (35.4 per cent) of whom showed silicosis. The first stage developed after five years of exposure and the third stage in ten to fifteen years. It developed in severe form in about twenty years. In this latter instance the far advanced cases were present in the most productive age group. The problem of silicosis in the iron ore mines has been present in Sweden for the past forty to fifty years, since the introduction of the machine drill. First stage of silicosis was seen to develop after a five year employment in the Lapland mines. All iron ore miners in middle Sweden showed evidence of silicosis after forty years of exposure. The author found no close relationship between tuberculosis and silicosis in the iron ore miners. Comparing silicosis in different industries in Sweden, the author found that severe silicosis occurs most rapidly in quartz-mill workers, sand streamers, drillers in quartz mines and cast-iron polishers, all of whom developed third stage silicosis before fifteen years of occupation. In oven masons and drill borers and in iron-ore miners at least fifteen to twenty years of exposure is necessary, while in porcelain workers at least twenty-five years of exposure is required for silicosis to develop. The material does not allow to draw any definite conclusions as to the rôle of tuberculosis in silicosis. Although each individual in whom a diagnosis of silicosis

was made had roentgenographic findings common to them all, each group had distinctive characteristics which are so typical that even without knowledge of the occupational history, a definite conclusion may be made as to the type of work in each case. Bronchographic studies were performed to study the topography of the bronchial tree, which is related to the contracting foci in the lung in silicosis in the third stage. The contracting centre exercises its pull on the most ventral bronchi and they are dislocated upward and anteriorly. The position of the dorsal bronchi is influenced only to a small degree. The contrast substance in the bronchi stops at the homogeneous areas, indicating that the bronchi are squeezed off in the region of the massive density. Bronchspirometric examinations were performed on 197 cases; 48 in the first stage, 68 in the second stage and 84 in the third stage. The spirometric changes in severe silicosis showed definite differences between cases in which the course of the disease is more rapid and those in which the development of silicosis is slower. In the slower development of third stage silicosis, the increase of residual air is significant and the total capacity is not greatly decreased. In the more rapid progression of the disease, the limitation of the total capacity in the third stage is marked, while the residual air is not changed. Bronchspirometric examinations in far advanced cases show that part of both lungs share in the oxygen intake and carbon dioxide output and that minute ventilation and vital capacity lie within normal limits. The author believes that respiratory insufficiency is the result of the emphysematous transformation which characterizes the advanced stage of silicosis.—*Die Silikose als Berufskrankheit in Schweden, T. Bruce, Acta med. Scandinav., Supplement 129, 1942, pp. 333.*—(O. Auerbach)

**Zinc Chloride Smoke.**—Zinc chloride smoke is said to be innocuous in the open, but its inhalation in confined spaces is extremely serious. Aside from the high temperature of the inhaled particles the hygroscopic and astringent properties of the substance are

dangerous irritants in the respiratory passages. Because of the particulate nature of the smoke, damage to the lungs is relatively slight. In an accident in Malta, 70 people were exposed to zinc chloride smoke in a tunnel. A total of 10 deaths following exposure was recorded, either immediately or within a week. The immediate effects consisted of dyspnea, stridor, cough, bloody expectoration, retrosternal constriction and pain. There was pale gray cyanosis which was only partially relieved by oxygen. Outpouring of secretions was a marked feature of the illness. Two autopsies were done. These showed edema and ulceration of the tracheobronchial tree leaving large denuded areas. The lungs showed patchy bronchopneumonia and engorgement. The uninvolved lung was emphysematous, and congestion and subpleural hemorrhages were noted. The intense heat of the particles had also caused external burns. Treatment was entirely symptomatic.—*Casualties following Exposure to Zinc Chloride Smoke, E. H. Evans, Lancet, September 22, 1945, 249: 368.*—(H. Marcus)

**Familial Spontaneous Pneumothorax.**—Two brothers suffered from a spontaneous pneumothorax at the age of 36 years. One sustained a sudden left pneumothorax during an attack of what was thought to be influenza and tonsillitis. He developed slight fever and on fluoroscopic examination a total collapse of the left lung was found with a small amount of fluid in the costophrenic angle. All laboratory and clinical investigations to determine the origin of his infectious state were negative. The lung reexpanded completely in two months. This patient had been under observation for several years before this accident. In none of the X-ray plates before and after the spontaneous pneumothorax could any pulmonary lesion be found. The brother suffered for one and one-half months of slight thoracic pains which could at first not be localized but which finally settled in the base of the right hemithorax. An X-ray film showed a small marginal pneumothorax on the right which was notable for the complete

absence of any adhesion. The lung tissue was completely transparent. There was a small amount of fluid in the costophrenic angle. He had neither dyspnea nor cough and recovered within six weeks, during which time he had a slight elevation of temperature. This patient also had had previous and repeated X-ray films after the accident. All proved to be completely negative. A few cases of idiopathic familial spontaneous pneumothorax have been described in the literature. In some of them the pneumothorax has lasted as long as twenty years. Generally, a complete absorption of pneumothorax air takes place in six weeks. The concept that every spontaneous pneumothorax is caused by tuberculosis must be abandoned. Almost all cases of spontaneous idiopathic pneumothorax are in male patients. The intrapleural pressure generally remains negative and, if positive, does not reach more than plus 2 to plus 5 or rarely plus 10. The pneumothorax is produced by an accidental rupture of subpleural blebs of a special structure in the presence of a familial predisposing factor.—*Neumotorax espontaneo idiopatico familiar, H. Orrego Puelma & L. Richard B., Prensa méd. argent., July 6, 1945, 32: 1252.*—(W. Swienty)

**Spontaneous Pneumothorax.**—A 21 year old soldier gave a history of frequent mild upper respiratory infections. An X-ray film of the chest revealed no abnormality in September, 1944. In September, 1945, while he was flying for the first time in an airplane, he experienced pain in the upper right thorax. The altitude of the flight was approximately 8,000 feet. Six days later the pain was still present and the patient sought medical advice. Physical and roentgenological examination revealed 60 per cent collapse of the right lung.—*Spontaneous Pneumothorax Produced by Ascent in an Airplane, H. V. Holler & O. Horwitz, J. A. M. A., March 3, 1945, 127: 519.*—(H. Abcles)

**Spontaneous Pneumothorax.**—Pulmonary tuberculosis is thought to stand first as the exciting cause of spontaneous pneumothorax

while other forms of pulmonary disease may result in spontaneous pneumothorax. It also occurs in apparently healthy persons and as the result of extrapulmonary conditions. However, it is considered rare as a complication of pneumonia in adults, most persons assuming that pneumonia results in complications conducive to pneumothorax. A review of literature, which is scant, shows the earliest reference to this is by Van Mering, reporting 2 cases of spontaneous pneumothorax occurring in pneumonia. Various authors subsequently reported cases of pneumonia complicated by pneumothorax, a total in all of 20 cases. The author believes that it occurs more frequently than previously believed and presents reviews of 2 cases. In the first patient, pneumothorax was discovered in routine X-ray examination. The second was discovered when the patient again developed fever and examination revealed hyperresonance and diminished breath sounds. Fluid was also present. Culture was negative for any organisms. Autopsy revealed a partial collapse of the lung and also endocarditis. In neither case was there any evidence of tuberculosis. The fact that pneumothorax may be masked by the other grave symptoms of pneumonia may account for failure of more frequent recognition.—*Spontaneous Pneumothorax as a Complication of Pneumonia in Adults, E. R. Movitt, Am. J. M. Sc., May, 1945, 209: 595.*—(G. F. Mitchell)

**Pneumothorax from Gastric Ulcer.**—This condition is rare and has been reported in 25 cases to date. The usual course of events is rupture of a gastric ulcer at the cardiac end of the stomach into the peritoneal cavity with the formation of a subphrenic abscess and erosion into the pleural cavity through the diaphragm. In the present case, an ulcer in the cardia dissected through the coats of the stomach and esophagus and ruptured into the left pleural cavity without touching the peritoneal cavity. Contents of the left hydropneumothorax were aspirated and were clearly shown to be gastric juice. The patient died fourteen and one-half hours after admission to

the hospital and the findings at autopsy confirmed the diagnosis.—*Pneumothorax Resulting from a Dissecting Gastric Ulcer*, P. B. Hudson, L. C. Gray & H. E. Newman, *Arch. Surg.*, June, 1945, 50: 501.—(H. Marcus)

**Blast Injury.**—It has been fairly well ascertained that according to their severity the lung lesions resulting from blast are: (1) a few small hemorrhages on surfaces of lungs; (2) patchy hemorrhages throughout the lungs; (3) complete hepatization of the lungs by hemorrhages. Further accepted is the direct etiology of blast injuries—by the wave of positive pressure acting directly on the chest wall. In this series 21 cases on nonpenetrating blast injuries unaccompanied by additional trauma were studied. It was possible to observe cases at different intervals after injury and watch their progress for a few days before sending them on to base hospitals. With few exceptions the blast—in these cases—seemed to have been sustained chiefly by the chest, and, conversely, cases of abdominal blast—not included in this series—were noticeably free from pulmonary symptoms. There was complete calm in these patients—no evidence of anxiety or overreaction. Over half the patients were unconscious for a few minutes to several hours after injury. No abnormal central nervous system symptoms or signs were noted. Dyspnea was universal—sometimes described as “tightness” and a “blown-up feeling.” Rapid wheezing respirations, coughing of frothy blood-stained sputum and sometimes cyanosis were recorded. Pain was a constant feature; two types being present: (1) retrosternal pain, and (2) muscular. Cough occurred in all but 2 cases and hemoptysis in 15. Except for generalized rhonchi which cleared in a few days and a few cases of massive involvement showing dullness, diminished breath sounds and fremitus, the physical signs were sparse. Ten of the cases showed no detectable abnormality in chest films taken within a few days of injury. There was nothing specific about the shadows of the radiologically positive cases; they were unilateral in some instances, bilateral in others; and varied from

increased density to the appearance of massive consolidation. All opacities were in the middle and/or lower zones, situated for the most part centrally. The shadows were confluent and not patchy. There seemed to be little correlation between the severity of the symptoms and the amount of damage as revealed by X-ray films. Of the 15 cases with hemoptysis only 6 showed radiological changes. Considering this discrepancy it seems possible that the source of bleeding in those patients with clear films may be bronchial. Treatment should be for the symptoms—rest and physiotherapy for the muscular pain.—*Blast Injury to the Lungs—Clinical and Radiological Findings and Their Relation to Certain Symptoms*, G. R. Fearnley, *Brit. M. J.*, April 7, 1945, 1: 474.—(D. H. Cohen)

**Right Heart in Pulmonary Disease.**—It has been stated that fully 10 per cent of all cases of chronic cardiac failure are secondary to disease of the respiratory system. Electrocardiographic evidence of right ventricular preponderance, of hypertrophy of the right heart, of insufficiency of the right coronary artery should immediately stimulate an investigation of the lungs. Pulmonary functional damage is not always demonstrable in the X-ray film, and in the absence of obvious mitral or congenital heart disease, the respiratory tract must be held responsible for the alterations of the right myocardium. Abnormal resistance in the lesser circulation is the immediate precursor of right cardiac hypertrophy, right coronary sclerosis and myocardial insufficiency. This picture is frequently well developed in young people in whom a rheumatic etiology is sought for in vain. Inasmuch as no demonstrable cardiac hypertrophy may accompany this picture of right heart failure, the recognition of the electrocardiogram of right heart strain and insufficiency is of extreme importance to the clinician in diagnosis and prognosis.—*Myokardschädigung des rechten Herzens als Folge Pulmonaler und pleuraler Affektionen*, E. Attinger, *Schweiz. med. Wchnschr.*, November 8, 1945, 75: 969.—(H. Marcus)



**Infarct Cavities.**—Although pulmonary infarction in the course of cardiac disease or postoperatively is not uncommon, necrosis of the infarct with cavity formation is rare. In 104 cases of pulmonary infarction which came to autopsy, only 6 cavities were found. Predisposing causes for the formation of cavity are the size of the infarct, which is usually large, location in the upper lobes, and pre-existing disease of the pulmonary arterial system, such as arteriosclerosis, arteritis, or changes due to chronic interstitial pneumonia. Pyogenic infection of the infarct by the bronchial route is the final and decisive factor. Clinical diagnosis of infarct cavity is difficult. The patients are usually desperately ill. It is difficult to get a good X-ray film, and hardly ever is the patient well enough to sit up, so a fluid level in the cavity might be demonstrated. The outcome is that of the primary disease, and therefore often fatal. Histologically the cavities are large, cone shaped, with the base of the cone at the pleura and the apex to the hilum. Four distinct layers may be recognized. The inner necrotic layer contains elements of lung tissue, and the elastic framework of the lung can be recognized. Around this a leucocytic collar is usually seen, then a layer of granulation tissue, and a surrounding area of pneumonia. The main pulmonary arteries are plugged by emboli.—*Ueber die Infarktkaverne der Lunge, M. Aufdermaur, Schweiz. med. Wchnschr., November 18, 1944, 74: 1191.*—(H. Marcus)

**Bronchogenic Carcinoma.**—Bronchogenic carcinoma is one of the most frequent and important primary malignant lesions. It is second only to carcinoma of the stomach according to autopsy findings. The incidence is increasing both relatively and absolutely. Dorn estimates that of 450,000 to 500,000 individuals in the U. S. under medical care for carcinoma, 13,000 are being treated for carcinoma of the lung. Approximately 8,000 new cases of carcinoma of the lung are diagnosed each year. The greatest incidence is in males in the fifth, sixth and seventh decades. McAlldowie reported a case in a 5½

months old child. Repeated inhalations of smoke produce chronic irritation of the bronchial mucosa as evidenced by the characteristic associated cough. The increased incidence of bronchial carcinoma directly parallels the increased sale of cigarettes. Pulmonary carcinoma is almost entirely a disease of the bronchi, beginning only rarely in the alveoli. It occurs more often on the right side than on the left side. In Ochsner's series of 52 pneumonectomies, the right upper lobe was involved in 25 per cent, right lower lobe in 25 per cent, right middle lobe in 3.8 per cent, the left upper lobe in 19.2 per cent, and the left lower lobe in 13.5 per cent. The region of the hilum is most frequently involved. Growth is relatively slow. Localization persists for a considerable period. Wegelin found 11 per cent with no evidence of extension even at time of autopsy. Metastasis is by direct extension, intrabronchial spread, implantation by aspiration, biopsy, or operation or by hematogenous or lymphogenous routes. Metastases constitute the most important single prognostic factor. Regional bronchial and mediastinal nodes are the most frequent sites. In Wegelin's series lymphogenous metastases were present in 81.2 per cent. Ochsner reported 3,047 collected cases with metastases as follows: 72.2 per cent to the regional lymph nodes, 33.3 per cent to the liver, 29.8 per cent to the pleurae, 23.3 per cent to the contralateral lung, 21.3 per cent to the bones, and 20.3 per cent to the adrenals. Of 116 cases reported by Ochsner, 90, or 77.6 per cent, were considered operable. Of these, 52, or 44.8 per cent, had successful pneumonectomies. The balance were explored and found inoperable. There is no typical clinical picture. The onset is usually insidious. There is often an antecedent history of respiratory infection, so-called flu, from which recovery was never complete. Cough is the most frequent symptom, occurring in from 65 to 91 per cent in various series. In Overholt's series 63 per cent had been incorrectly diagnosed by the first physician consulted. There may be no chest symptoms present or epigastric distress, anorexia, nausea, vomiting, malaise or weight loss may occur.

Expectoration is rather frequent and is especially important when associated with hemoptysis. Hemoptysis was the chief complaint in 18.9 per cent of Ochsner's series, but was present at some time in 48.3 per cent. Thoracic discomfort may occur. Dyspnea is infrequent and late. The interval between onset of symptoms and death is relatively short, from less than one month to fifteen months in the literature. The authors point out that the growth may exist for a long period before symptoms are present. The diagnosis is not difficult if suspected in every male over 40 years of age with unexplained respiratory or digestive complaints. The X-ray may be negative early because of the difficulty in differentiating hilar shadows. Andrus found X-ray gave the correct diagnosis in 58, or 90.6 per cent, of 64 cases. Bronchoscopy is the most reliable method and should give a positive diagnosis in 70 per cent because that is approximately the incidence of hilar involvement. Holinger and Hara obtained positive diagnoses by bronchoscopy in 78.4 per cent. Hilar lesions in the upper lobe bronchus may be beyond the vision of the bronchoscope. In the author's series of 52 pneumonectomies the clinical findings were positive in 100 per cent, radiological findings in 44.2 per cent, positive biopsy by bronchoscopy in 32.6 per cent. Bronchoscopy had been done in 46, or 88.4 per cent, of these 52 cases. However, biopsy was possible in only 23 of the 46 cases. Of these 23 biopsies, the diagnosis was positive in 73.9 per cent. Bronchography and examination of sputum and pleural fluid for tumor cells may also be helpful. The authors are unequivocally opposed to aspiration biopsy because of the danger of implantation metastases. They had 2 such cases in this series. Surgical extirpation is the treatment of choice. Irradiation is of little value except to relieve manifestations in hopeless cases. Pneumonectomy should be performed even if the lesion is limited to a single lobe. Preliminary pneumothorax is desirable, gradually increasing the intrapleural pressures to the positive side. This manoeuvre determines the presence, extent and location of adhesions, compresses the

pulmonary bed gradually allowing the cardiovascular system to compensate. This is especially important in patients with limited cardiac reserves. Age in itself is no contraindication to pneumonectomy. Inhalation cyclopropane is the anesthesia of choice using positive pressure. A trained anesthetist is of the utmost importance. At least 1,500 cc. of blood should be available for each case. The anterior approach is preferable because it allows freedom of cardio-respiratory function. The postero-lateral approach offers the advantage that dense posterior and lateral adhesions can be divided under direct vision. Pleuralization of the bronchial stump is probably the most important manoeuvre in preventing insufficiency of the stump. Closure should be without drainage. Immediate post-operative bronchoscopy to aspirate secretions is advised. Oxygen should be given for twenty-four hours postoperatively. Early ambulation is important. Of 361 collected cases of pneumonectomies for primary bronchogenic carcinoma, 51.5 per cent are living and 48.4 per cent are dead. Of the authors' 52 cases, 22, or 42.3 per cent, are living, 57.5 per cent are dead. Of those still living, one is living eight years after operation, 1 six years, 2 five years, 2 four years, 3 three years, 1 two years, 6 one year, and 6 less than one year.—*Primary Bronchiogenic Carcinoma, A. Ochsner, J. L. Dixon & M. DeBakey, Dis. of Chest, March-April, 1945, 11: 97.*—(K. R. Boucot)

**Bronchoscopy in Carcinoma**—The increasing frequency of bronchial carcinoma and the better results of surgery as compared with radiotherapy, necessitate exact localization of the lesion. For such localization bronchoscopy is used most often and is the most exact inasmuch as it allows biopsy at the same time. The author reports a study of 308 cases which came to autopsy between 1927 and 1943. Two hundred seventy-three were males and 35 females, a ratio of 7.8:1. In 11 the primary site was unknown, in 2 the lesion was at the bifurcation, in 132 on the left and in 163 on the right. Seventy per cent were in the large

bronchi, the remainder in the periphery. Fifty-four per cent were oat cell carcinoma, 35 per cent squamous cell carcinoma and 10 per cent adenocarcinoma. Only 42 per cent were seen on direct view. This included those at the bifurcation, main bronchus or stem bronchus. The remainder of those in the large bronchi had to be visualized with mirrors.—*Zur Frage der Leistungsfähigkeit der Bronchoskopie für die Diagnostik der Bronchialkarzinome*, I. A. B. Cathic, *Schweiz. med. Wchnschr.*, January 6, 1945. 75: 15.—(J. Gerstein)

**Disturbance of Pigmentation with Pancoast Tumor.**—Disturbances of pigmentation in the presence of involvement of the sympathetic nervous system have only rarely been reported. The present report deals with a 47 year old woman who was observed for one and one-half years until she died of a superior sulcus tumor. She had typical involvement of the sympathetic ganglia and trunk, with miosis and anhidrosis. When ultraviolet radiation was given, it was noted that the affected side failed to show skin pigmentation equal to the unaffected side. The line of pigmentation was strictly limited by the midline, and although the face and neck did show some pigmentation later on, the difference on the chest and back remained marked until the time of death. This patient had extensive metastasis to the ribs and vertebral column, but in view of the fact that no corresponding large areas of loss of sensation were present, the author attributes the failure of the skin to show pigmentation following ultraviolet radiation to involvement of the sympathetic nervous system rather than to metastasis to the central nervous system.—*Über einen Fall von Pancoast's Syndrom mit neurogener Herabsetzung der Pigmentierungsfähigkeit*, G. Lindgren, *Acta med. Scandinav.*, June 23, 1942, 110: 445.—(H. Marcus)

**Pulmonary Alveolar Tumors.**—Pulmonary alveolar tumors are considered rare. However, its infrequent observation may result from the difficulty of premortem X-ray and

clinical diagnosis. Therefore, 6 cases of probable alveolar tumors are presented, and the differential diagnosis from bronchogenic and metastatic tumors and from infections discussed. Disease may be of predominantly nodular or diffuse form, often with widespread metastasis. Symptoms are those of pain, cough, weakness, weight loss and dyspnea. Bronchoscopy is usually negative. It may be complicated by other conditions, such as pneumonia. One case was complicated by *Torula histolytica* infection and had predominating cerebral and meningeal symptoms. All died and microscopic sections of the tumors favored the alveolar wall as the origin of tumor. Some would dispute this, but only serial sections through the lungs would make diagnosis absolutely irrefutable. A review of literature disclosed 24 clear-cut cases from the world literature. While most of these tumors have been definitely malignant, some were borderline or histologically benign. The clinical features as reported are similar to other lung tumors, such as, cough, cyanosis, bloody sputum, chest pain, pleural effusion and, in some cases, central nervous system symptoms. Even cases histologically benign had a fatal outcome due to the extent of the involvement and secondary infections, so that the prognosis is unfavorable in the majority of cases. Unilateral diffuse monolobar tumors may be amenable to surgery or X-ray treatment. The X-ray appearance suggests the difficulty of conclusive diagnosis, because alveolar tumors may simulate bronchogenic cancer, metastatic tumor, fungus or tuberculous infection and pneumonitis. Complications, especially pleural effusion, bronchiectasis and cavity add to the confusion as they may be the direct result of the tumor or may be purely incidental. While tumor was the definite diagnosis in 5 of the 6 cases, the true character of the tumor could not be determined. Some of the older cases in literature were misdiagnosed as tuberculosis or pneumonia. The absence of fever, weight loss, progressive weakness, may favor diagnosis of tumor, but, with our present knowledge, the differential diagnosis in the majority of cases can only be made

on microscopic examination. However, in all patients with multiple nodular, apparently metastatic nodules without evidence of neoplasm elsewhere, such diagnosis should be considered.—*Roentgenologic Aspects of Pulmonary Tumors Probably Alveolar in Origin*, E. F. Geever, H. R. Carter, K. T. Neubeurger & E. A. Schmidt, *Radiology*, April, 1945, 44: 519.—(G. F. Mitchell)

**Pulmonary Sarcoma.**—The case history of a 66-year-old female patient is given. The onset of her illness was in January, 1944, with pain in the left chest. In May, 1944 she developed dyspnea. Roentgenological examination in June, 1944 revealed opacity of almost the entire left lung field. On bronchoscopy a gray mass was seen in the left main bronchus and the diagnosis of a polyp was made. Histological examination of the mass did not decide the diagnosis. After bronchoscopic removal of the tumor the left lung became again aerated and the patient's condition improved. One month later the symptoms had reappeared. Bronchoscopy revealed recurrence of the mass, which could not be removed completely this time. A histological diagnosis was again impossible. Pneumonectomy was considered but not done because of the age and the general condition of the patient. Six weeks later she was again bronchoscoped and on biopsy the diagnosis of fibrosarcoma was made. The patient died in December, 1944, under the symptoms of extreme dyspnea. At autopsy a fibrosarcoma was found which occluded the left main bronchus completely, and partially the orifice of the right main bronchus. There were no metastases. The rarity of pulmonary sarcoma is stressed.—*Un cas de sarcome primitif du poumon*, G. L. Colé, *Laval méd.*, September, 1945, 10: 487.—(G. C. Leiner)

**Metastatic Hypernephroma.**—Although hypernephroma is known to metastasize to the lungs and mediastinal lymph nodes with some regularity, it is uncommon to find that the pulmonary metastasis is the presenting symptom. Only a few cases have been reported in

the literature where the pulmonary metastasis caused the death of the patient and a renal tumor could be found at autopsy only. It is well known that hypernephromata may remain small yet metastasize widely. The chest X-ray film shows a picture of mediastinal lymph node enlargement which is progressive and the later development of pulmonary lesions. The differential diagnosis from malignant lymphomata is difficult, if not impossible. When it is imperative to make a diagnosis from the point of prognosis, transpleural biopsy of the mediastinal lymph nodes is suggested.—*Intrathoracic Hypernephroma Metastases Simulating Primary Pulmonary Disease*, S. Radner, *Acta med. Scandinav.*, October 28, 1942, 112: 264.—(H. Marcus)

**Lung in Leukemia.**—Pulmonary infiltrations in leukemia were first described in 1885, after autopsy. Clinical discovery is much more difficult. Joachim and Loewe, in 1927, described a case of myelogenous leukemia, in which X-ray films taken every fifteen days showed transitory pulmonary infiltrations. Dyspnea and hemoptysis were present. On autopsy there were found subpleural nodules of myeloid tissue, 2 to 5 cm. in diameter. The author describes a case of acute myelogenous leukemia which was followed from the start, and which showed consolidation in the right upper lobe, and crepitant râles, but no symptoms referable to the lungs. This progressed until there were signs of a cavity, which was confirmed by X-ray film. On autopsy myeloblasts were demonstrated in the bronchial and alveolar walls, with occlusion of the capillaries by myeloblasts. Leukemic infiltrations were also found in the skin, buccal mucosa, myocardium, kidneys, spleen, liver, lymphatic tissue, intestines, tonsils and testicles.—*Le poumon leucémique*, H. Dubois-Ferrière, *Schweiz. med. Wchnschr.*, January 6, 1945, 75: 11.—(J. Gerstein)

**Hydatid Cyst of Pericardium.**—Hydatid disease of the heart is observed in 0.7 to 13.6 per cent of all cases of hydatid disease. Review of the literature shows that there are only

50 cases of hydatid cyst of the pericardium. The authors present one case. A laborer of 35 years was complaining of dyspnea on exertion and circulatory disturbances which had increased during a period of three years. He had suffered several attacks of violent pain in the lower part of the right hemithorax radiating into the right arm. The X-ray revealed an opaque density in the right cardio-phrenic angle; its outline was rectangular. An oblique X-ray film showed that its location was anteriorly and above the diaphragm. It did not move with the diaphragm. The laboratory tests showed a strongly positive Casoni reaction and eosinophilia of 6 per cent. The diagnosis was based entirely on these findings. The difficulty was to localize the cyst exactly. The margin of the inferior lobe of the lung, the convexity of the liver (with perforation of the diaphragm), the diaphragm, the mediastinum and the pericardium were possible localizations. An operation under local anesthesia was done. The incision was made along the sixth rib anteriorly with resection of a portion of that rib and all of its cartilage. The cyst was visualized but no pleural adhesions were found. It was decided to leave an iodoform gauze pack to establish adhesions. Two weeks later the wall of the cyst was incised and the liquid material aspirated. The cyst was found to be within the pericardium. Its walls could not be removed completely. The opening in the pericardium was not closed. The patient has since been checked at regular intervals and found to be in perfect health twenty-one months later. At this time the electrocardiogram showed a rotation of the heart. All other findings were normal. He still had 5 per cent eosinophils and a positive Casoni reaction. From that, the author concludes that there is a metastatic localization of the disease in other parts of the pericardium. In the differential diagnosis the following conditions have to be considered: (1) of cardiovascular origin: intrapericardial aneurysm of the aorta, aneurysm of the wall of the heart, dilatation of the left auricle, diverticulum of the pericardium, cystic pericarditis, lipoma of the pericardium; (2) of pulmonary etiology:

hydatid cyst, bronchial carcinoma, benign tumor, hemangioma, endothelioma, melanoma, metastasis of seminoma or hypernephroma, congenital cyst; (3) of the mediastinum: mega-esophagus, diverticulum of the esophagus, intramural tumor of the esophagus, basal mediastinal pleurisy, neurofibroma of the pleura, ganglioneuroma, cystic teratoma, tuberculoma, leukemia, aleukemia; (4) of diaphragmatic and subdiaphragmatic origin: hydatid cyst of the mediastinum, diaphragmatic hernia, hydatid cyst of the convexity of the liver, hydatid cyst of the diaphragm, lipomata and fibromata; (5) originating in the thoracic wall: chondroma, fibroma, osteoma, abscess, hydatid cyst, extrapleural hematoma, meningocoele. Pneumothorax, pneumoperitoneum and pneumopericardium are of value to establish the diagnosis. An exhaustive review of the literature is given.—*El hidatidoma pericardico*, J. G. Bengochea, *Rev. españ. de cir., traumatol. y ortop.*, May, 1945, 2: 277.—(W. Swienty)

**Isolation of Thromboplastin from Lung Tissue.**—Thromboplastin is a term applied to any substance, or any group of substances present in the tissues which initiate or facilitate the process of clotting. In the mammal we have the thromboplastic substance furnished by the platelets of the blood and by the extravascular tissues. There is general agreement that the largest concentration is found in the lungs. The nature of this substance has not been definitely settled. The author has endeavored to isolate and purify thromboplastin from lung tissue with two main objects in view: first, the development of a method for obtaining a usable preparation of thromboplastin to control hemophilic bleeding, or for application as a hemostatic agent, or as a reagent in the determination of prothrombin times and, second, to determine its chemical nature. Although thromboplastin in sufficient purity to determine its true chemical form was not procured, the crude material obtained appeared to be a protein compound of a phospholipid. Such material from human and pig lungs, specially treated, gave sub-

stances capable of clotting hemophilic blood in one to two minutes in concentrations of 1 mg. to 15 or 20 cc. of blood. This material can be kept in dry form in CO<sub>2</sub> with practically no loss of potency and, after sterilizing by heat, in alkaline solution in sterile serum tubes, with very slight loss of potency. The liquid material was used intravenously without serious reactions, the pig material in a strain of hemophilic swine, and the human material in a single clinical case. In the pigs the clotting time was reduced for a period of at least four hours. After twelve hours the blood returned to its usual clotting time, but after an interval of forty-eight to seventy-two hours there was again an unexplained marked and continuing reduction in clotting time. The human case, a patient bleeding profusely from aplastic anemia, received two injections intravenously, six days apart. The first injection was followed by a chill and the second by a rise in temperature. Nevertheless, the patient was favorably affected for the bleeding from the gums, pharynx and nose ceased and the blood coagulation time was shortened for a considerable period. There was no evidence of blood regeneration and death soon followed. These findings give a definite hope that material prepared in this form might be used to control hemophilic bleeding. Further purification of this crude material showed that it was possible to remove the protein, leaving a residue with marked thromboplastic activity, the chemical nature of which was not determined.—*The Isolation of Thromboplastin from Lung Tissue*, W. H. Howell, *Bull. Johns Hopkins Hosp.*, June, 1945, 76: 295.—(J. S. Woolley)

**Defect of Anterior Mediastinum.**—A 7-week old female infant was seen with episodes of cyanosis and rapid breathing. Roentgenological examination of the chest revealed an oblong, air-filled structure in the anterior upper portion of the right pleural cavity, which extended over behind the sternum to the left of the midline. The picture was suggestive of a congenital cyst of the right lung, communicating with a bronchus, and an anterior

mediastinal hernia. Aspiration of the cyst under fluoroscopic control resulted in bilateral pneumothorax. Exploratory operation revealed an emphysematous right upper lobe, which protruded into the left chest through an extensive defect of the anterior mediastinum. Because of the poor condition of the patient the chest was quickly closed. During the following years the patient had frequent episodes of dyspnea apparently due to a valve-like mechanism in the right upper lobe bronchus which permitted air to enter and to distend the lobe. At the age of 4 an operation was performed: the mediastinal defect was closed and the right upper lobe was removed. Following that the child was completely asymptomatic.—*Defect of the Anterior Mediastinum: Successful Surgical Repair*, R. E. Gross & J. E. Lewis, *Surg., Gynec. & Obst.*, May, 1945, 80: 549.—(G. C. Leiner)

**Dermoid Cyst of Mediastinum.**—A 32 year old woman, suffering from cough, was examined by fluoroscopy and a tumor was seen in the hilum. This did not change its shape during respiration, it had well defined, irregular contours and it was round. Its shadow was not uniform and in some places it was as heavy as the cardiac shadow. Differential diagnosis with lipomata, chondromata, fibromata, malignancies and hydatid cyst was considered. By puncture, sebaceous material was obtained. The clinical diagnosis of dermoid cyst was established.—*Quiste dermoideo del mediastino*, A. P. Heudtlass & J. A. Marti, *Bol. d. Hosp. F. Santojanni*, 1945, 1: 169.—(P. B. Franca)

**Sarcoidosis and Diabetes Insipidus.**—Although the occurrence of diabetes insipidus in tuberculosis is excessively rare, its occurrence in disseminated sarcoidosis is not infrequent. It is due to involvement of the posterior pituitary by specific granulomatous tissue. The symptom is transitory and tends to disappear as the generalized disease improves. In a recent case reported by the author, the superficial lymph nodes, the mediastinal lymph nodes, spleen, kidneys and myocardium were involved, and the patient also presented iritis

and parotitis. Disseminated sarcoidosis is a generalized disease of the reticulo-endothelial system probably caused by the tubercle bacillus. The fact that patients do not react to tuberculin should not be regarded as a true anergy. The response of the reticulo-endothelial system to the presence of the tubercle bacillus is apparently so prompt and vigorous that tubercle bacilli are immediately destroyed locally. Although there is some evidence to show that antibodies are produced in abundance, the theory advanced holds that they are fixed locally and that none are, therefore, available for a positive cutaneous reaction. It is not unusual to find the tuberculin test becoming positive as the sarcoidosis undergoes healing. This may be the case although there is no evidence of caseous tuberculosis anywhere in the body. Hyperplasia of the reticulo-endothelial system appears to be responsible for the hyperglobulinemia which is seen with some degree of regularity. A specific effect on the mineral metabolism by the reticulo-endothelial cells is claimed to account for the presence of hypercalcemia. There are three forms of tuberculosis which involve the lymphatic and hemopoietic systems specifically without a tendency to develop into banal progressive organ tuberculosis. Sarcoidosis represents the benign form in which the prognosis is favorable due to a good immunological balance. The second disease, generalized caseating tuberculosis of the lymphatic and hemopoietic systems, is a serious disease with an intermediate antibody response. Recovery from this disease is possible. The third form is acute tuberculous sepsis which is always fatal. In this disease the tuberculin test is also negative, but here a true anergy is present. A specific tissue response is altogether absent and the lesions are widely scattered caseous necrotic foci in which tubercle bacilli are found in great abundance.—*Diabetes insipidus bei der epithelioidzelligen Granulomatose, St. J. Leitner, Schweiz. med. Wchnschr., June 9, 1945, 75: 511.*—(H. Marcus)

**Splenomegaly in Sarcoidosis.**—A case of sarcoid is described, in which splenomegaly

was great enough to be symptomatic. Splenectomy was necessary. The spleen was adherent to the transverse mesocolon and parietal peritoneum and weighed 1,700 g. The capsule showed some dilated vessels and hemorrhagic foci. The outer part of the organ no longer showed normal splenic tissue. There were large nodules of epithelioid cells, separated by lymphocytes, red cells and bundles of collagen. The epithelioid cells were clear, with pale protoplasm and ill-defined borders. There were no true Langhans cells, though occasionally there were protoplasmic masses with six to eight nuclei in the centre. The centre of the nodule was often pierced by a terminal arteriole and the margin often crowned by lymphocytes. Collagenous tissue, frequent in the internodular area, occasionally ramified through the nodules, breaking them up into small collections of epithelioid cells. In the centre of the spleen the basic lesions were the same, though the sclerosis was more wide-spread and the nodules smaller.—*Splénomégaties et maladie de Besnier-Bocck-Schaumann, L. M. Pautrier, Schweiz. med. Wchnschr., August 26, 1944, 74: 907.*—(J. Gerstein)

**Liver in Mononucleosis and Sarcoidosis.**—In many diseases valuable information can be derived from aspiration biopsy of the liver and study of the tissue after fixation in formalin. In a case of infectious mononucleosis, biopsy showed proliferation of monocytoïd cells among the liver cells. The latter cells also showed some mitotic figures, and the picture somewhat resembled that of a myeloid leukemia. Repeated biopsy after three and one-half weeks showed restoration of the normal liver architecture. In 4 cases of sarcoidosis liver biopsy showed the presence of submiliary, noncaseous epithelioid tubercles in 2 instances. These tubercles were most commonly seen in the portal areas.—*Aspiration-biopsy of the Liver in Mononucleosis infectiosa and in Besnier-Bocck-Schaumann's Disease, Cornelia van Beek & A. J. Haax, Acta med. Scandinav., 1943, 113: 125.*—(H. Marcus)

**Brucellosis of Spine.**—The frequency with which brucellosis affects the bones and joints is becoming evident with improving laboratory tests and roentgenographic examinations. A case is reported which at first was considered as Pott's disease because X-ray films revealed a destructive lesion of the third and fourth vertebral bodies and the discs together with calcifications in the right lung. After the Mantoux reaction was found to be negative to 1.0 mg. of tuberculin, a series of laboratory investigations revealed that *Brucella suis* was the etiologic agent. The patient was a swineherd.—*Espóndilo-artritis brucelósica interpretada al principio como un mal de Pott*, R. Posse, *Rev. Asoc. méd. argent.*, January 15-50, 1945, 59: 58.—(R. Kegel)

**Erythema Nodosum.**—On the basis of the literature and of the observation of 24 patients with erythema nodosum—4 of whom are described in detail—the authors draw the following conclusions: Erythema nodosum in the child is almost always of tuberculous nature. In 90 to 95 per cent of the cases it occurs at the time of the primary infection. In the young adult, it is usually seen during the course of the primary infection, rarely in reinfection tuberculosis. Many other infections and intoxications can produce erythema nodosum. When a patient with erythema nodosum is seen, tuberculous etiology should be considered first, and this diagnosis should be maintained until proved otherwise. In every patient with erythema nodosum roentgenologic examination of the lungs should be done.—*Erythème noueux et tuberculose*, R. Desmeules & P. Richard, *Laval méd.*, September, 1945, 10: 478.—(G. C. Leiner)

**Etiology of Erythema Nodosum.**—Among the theories on the etiopathogenesis of erythema nodosum, the one considering this disease as caused by tuberculosis finds most credit at present. Its specific nature due to an unknown virus is also sustained by some, while others claim that it is an aspecific cutaneous manifestation elicited by various toxic-infective or parasitic agents. Clinical

observations, positive tuberculin reactions, correlated X-ray findings and rigorously conducted bacteriological studies speak in favor of the tuberculous etiology of erythema nodosum. There are various etiopathogenetic modalities through which tuberculosis might cause erythema nodosum. Since the existence of a filtrable form of tubercle bacilli has never been demonstrated with scientific certainty, the author feels that its rôle in the causation of erythema nodosum can be discarded. The following studies purport to decide whether erythema nodosum is a cutaneous manifestation of a paucibacillary tuberculous infection with only inflammatory and nonfollicular lesions, or whether it has to be considered as an allergic phenomenon of a predominantly, or exclusively, tuberculous origin. Sacenz insists on the necessity of employing only rigorously scientific procedures in the demonstration of tubercle bacilli in the expectoration, gastric contents, blood or biopsy material obtained from individuals with erythema nodosum. He rejects the results obtained by the method of "reinoculation and passage in series in guinea pigs" as inconsistent with the known facts. These studies were made on 41 children from 2 to 14 years of age, with a maximum incidence around 8 years of age, without preference for any sex. Erythema nodosum often occurs in individuals with endocrine disturbances, sometimes several members of the same family are affected and most cases are observed in the latter part of winter or in spring, a season which is favored also by tuberculous spreads. The examination of the gastric contents for tubercle bacilli resulted in positive cultures on guinea pigs in 24 cases out of 41 cases. In 21 cases with positive gastric contents there were significant X-ray findings. The demonstration of tubercle bacilli in the blood of these patients was successful in 5 cases out of 29. The relative rarity of positive blood culture is consistent with the conception of erythema nodosum as a syndrome related to the primary infection, the bacillemia in which is characterized by its early occurrence, its fugacity and by the small number of circulating bacilli. These bacteriological findings



constitute an argument in favor of the existence of bacillemia coinciding with the onset of the initial follicular lesion and the appearance of tuberculin sensitivity. Bacillemia under these circumstances has no prognostic significance. The presence of acid-fast bacilli was demonstrated only in 2 out of the 29 biopsies. It is noteworthy that the histological characters of the lesions were quite identical in both the negative and the positive biopsy cases. Much higher incidences of positive biopsies were reported by other authors, but the correctness of their method (reinoculation and passage in series in guinea pigs) is highly questionable. The fugacity, the symmetric bilateral character and the histopathological picture of the nodules, as well as the bacteriological findings, are all arguments against the assumption that erythema nodosum is a local skin tuberculosis. On the other hand, there are valid arguments in favor of the conception of erythema nodosum being an allergic manifestation of tuberculous nature. These are as follows: the possibility to produce the nodules experimentally by intracutaneous or hypodermic injection of tuberculin; the fugacity of the nodules corresponds closely to the course of an intensively positive tuberculin reaction; the multiple bilateral occurrence of the nodules is a common character of allergic phenomena; the histopathological picture of the nodules is the same observed in positive tuberculin reactions; the absence of acid-fast bacilli is the rule in all specific allergic reactions. It cannot be denied that erythema nodosum may be caused by allergens other than tuberculin. It is well to remember, however, that a negative tuberculin reaction does not exclude an allergic state: some unknown endocrine or sympathetic factors might prevent the allergic state from becoming manifest.—*El problema etiologico del eritema*

*nodoso*, A. Saenz, *Hoja tisiol.*, September, 1944, 4: 219, and December, 1944, 4: 331.—(L. Molnar)

**Erythema Nodosum.**—The author has observed 19 cases of erythema nodosum during the past two years. All cases occurred in women, and most of these were middle aged. This is in contradistinction to the usual incidence of the disease. All patients had a rather characteristic clinical picture starting with the complaint of sore throat. This was followed in three to five days by painful and swollen joints. The rash did not appear until the eighth to the fourteenth day of the illness. Temperature was almost uniformly high and 3 patients were critically ill. There was moderate leucocytosis with a normal differential count. Chest roentgenograms were entirely negative, but in 9 patients throat cultures were positive for hemolytic streptococci. Seven out of these 9 patients showed a high titer of antistreptococcus agglutinin. Mantoux tests were done in 5 patients, and were negative in 2 and faintly positive in 3. All patients made a complete recovery but the course was quite prolonged in some. The majority were well within two to four months, although some patients were well within three weeks. None of the patients developed evidence of tuberculosis while under observation in the out-patient department. Although the clinical picture of this syndrome is sufficiently typical to make its recognition important, it is well established that this disease does not represent an entity. It is most likely an allergic reaction which may be produced by a number of microorganisms, among them hemolytic streptococci.—*Erythema Nodosum*, E. Frankel, *Lancet*, June 20, 1945, 248: 817.—(H. Marcus)

# BCG VACCINATION IN HOSPITALS AND SANATORIA OF SASKATCHEWAN<sup>1</sup>

A Study Carried Out by the National Research Council of Canada

R. G. FERGUSON<sup>2</sup>

Since the discovery of the tubercle bacillus by Koch six decades ago, tuberculosis death-rates, case-rates and infection have fallen.

Side by side with spectacular success in protecting the public, we have observed the sad spectacle of the unabated breakdown of persons caring for the tuberculous sick. This became particularly noticeable in Saskatchewan in the early "thirties" among sanatorium nurses and attendants and nurses-in-training in hospitals. Phthisiophobia was developing among sanatoria employees and student nurses, and their tuberculosis-conscious relatives were restive. The condition threatened the efficient prosecution of the antituberculosis campaign.

It was known that infection, as indicated by a positive tuberculin reaction, had fallen rapidly among Normal School students of the Province, from 76 per cent in 1921 to 23 per cent in 1931. These young teachers were known to originate from much the same family background as that of the student nurses, and were on this basis regarded as a comparable group in the matter of infectivity of home environment. Bearing this information in mind, it was considered that the rise in morbidity rate might be due to a larger proportion of negatively reacting persons entering the hospital and sanatorium environment. It was decided to check up on the preventive technique practiced in these infectious environments and to introduce periodical tuberculin testing and X-raying of nurses in the eight larger hospitals and exposed nurses and other employees in the three sanatoria of the Province.

The findings of this study after five years' observation were: (a) that about 80 per cent of each class of nurses entering training since 1934 have been negative to tuberculin; (b) that by far the highest incidence of tuberculosis occurred among exposed persons who had been negative to tuberculin on entering the environments; (c) it was also noted that despite improvement in instruction concerning preventive technique, and the provision of improved facilities for the practice of this technique, little or no improvement in the protection of the exposed persons appeared to have been accomplished.

A possible solution for the problem was suggested by a coincident experience. During the period 1933 to 1938 a controlled experiment in the protection of Indian infants by BCG vaccination, without segregation during vaccination, had been carried on in the Qu'Appelle Health Unit in Saskatchewan, under the direction of the National Research Council. As a result, it appeared that a reasonable measure of protection was afforded these infants by vaccination while

<sup>1</sup> Presented before the Medical Section at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 12, 1946.

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they remained in the infectious environment of their homes on the Reserves; the death-rate from tuberculosis among the vaccinated infants as compared with the control infants was in the ratio of 1:4. In view of this fact, it was proposed to the Council that an attempt be made to afford a similar protection to unavoidably exposed nurses and sanatoria employees in Saskatchewan, by means of BCG vaccination without segregation during the process of vaccination, that is, BCG vaccine to be administered after the negative reactor entered the infectious environment and while on duty. This proposal was accepted by the Council and as a result the work of vaccination was started in September, 1938.

Heimbeck, in a personal communication dated June, 1938, summarized his results with BCG vaccination up to May, 1938. He had been studying prophylactic vaccination with BCG at the Ullevaal Communal Hospital in Oslo since 1927. His observations were that the incidence among vaccinated nurses who became positive from vaccination had been much lower than among non-vaccinated negative controls. Among 341 made positive to tuberculin by vaccination there were 12 diseased and no deaths; while among 284 non-vaccinated negative controls there were 97 diseased and 12 deaths; among 668 nurses entering training with a positive tuberculin there were 22 diseased and no deaths.

It was considered that BCG vaccination of unavoidably exposed persons in the environments of the Saskatchewan General Hospitals, where 35 per cent of all negative reacting nurses became infected during the training period, and in the Saskatchewan Sanatoria, where the rate of infection of certain groups of employees for the first year of exposure was 60 per cent, would test the efficacy of this prophylactic.

In endeavoring to obtain suitable controls, the advice of the National Research Council's Panel on Tuberculosis was sought. Since, during the period of vaccination there would be relatively few nurses and sanatorium employees entering the Saskatchewan institutions who would not be vaccinated, the Panel was unable to suggest a wholly comparable group of adequate size. It was recommended that a comparison be made of the experience of the vaccinated with that of similar non-vaccinated negative persons entering the Saskatchewan institutions during the five-year period immediately preceding the initiation of vaccination, making due allowance for changing conditions. It had also been hoped that the trend in tuberculosis infection during a decade in the Saskatchewan institutions could be compared directly with that in the Winnipeg General Hospital, where vaccination was not practiced, but changes in the schedule of training in the latter made this inadvisable and, as a result, conclusions had to be based on a comparison of morbidity statistics, with due recognition of the difference existing between the groups. This course has been followed, but because true controls, in the accepted sense of the word, could not be obtained in sufficient number that term will not be used in the balance of this paper and reference will be made only to vaccinated and non-vaccinated negatives. The principles recommended by the Panel on Tuberculosis for the selection of cases and the treatment of the results obtained have been adopted.

The significance of the data was assessed by Bogen's method (1). The

BCG vaccine used was prepared by Dr. Armand Frappier, Director of the Institute of Microbiology and Hygiene of the University of Montreal. The dose given was 0.2 mg. of BCG in 0.2 cc. solution; 0.1 mg. administered intracutane-

TABLE 1  
*BCG vaccination among nurses in hospitals*

Nurses entering training—period 1934-1943

ACCEPTED FOR STUDY	NUMBER OF PERSONS	TUBERCULOSIS CASES	PER CENT WITH TUBERCULOSIS	PROBABLE ERROR	YEARS OBSERVED	AVERAGE YEARS OBSERVED
Nurses in eight Saskatchewan Hospitals:						
BCG vaccinated nurses.....	1,005	9	0.895	$\pm 0.2$	2,434.4	2.42
Negative to tuberculin on entrance—non-vaccinated...	759	29	3.82	$\pm 0.46$	1,926.9	2.54
Positive to tuberculin on entrance.....	278	3	1.08	$\pm 0.42$	688.1	2.47
Total in eight Saskatchewan Hospitals—1934 to 1943.....	2,042	41	2			
Nurses in Winnipeg General Hospital:						
Negative to tuberculin on entrance—non-vaccinated...	609	26	4.26	$\pm 0.55$	1,392.53	2.28
Positive to tuberculin on entrance.....	200	2	1.0	$\pm 0.47$	477.1	2.39
Total in Winnipeg General Hospital—1934 to 1943.....	809	28	3.46			
Saskatchewan Hospitals and Winnipeg General Hospital combined:						
BCG vaccinated nurses.....	1,005	9	0.895	$\pm 0.2$	2,434.4	2.42
Negative to tuberculin on entrance—non-vaccinated...	1,368	55	4.02	$\pm 0.36$	3,319.4	2.43
Positive to tuberculin on entrance.....	478	5	1.046	$\pm 0.31$	1,165.2	2.43
Total accepted for study in Saskatchewan Hospitals and Winnipeg General Hospital combined—1934 to 1943.....	2,851	69	2.42			

ously at each of two sites on the upper arm or thigh. Vaccination was instituted on the basis of a signed request by the individual desiring vaccination. Information up to March 31, 1945 is embodied in all these studies.

## EXPERIENCE IN EIGHT SASKATCHEWAN GENERAL HOSPITALS

All nurses entering training in these eight hospitals in the years 1934 to 1943, inclusive, are included in the study.

TABLE 2

*Incidence of infection of non-vaccinated negatives in hospitals*

Using only those negatives who had satisfactory tuberculin information

YEAR OF ENTERING TRAINING . . . . .	1934	1935	1936	1937	1938	1934-1938	1939	1940	1941	1942	1943	1939-1943	1934-1943
<b>Eight Saskatchewan Hospitals:</b>													
Number negative to tuberculin on entrance . . . . .	62	93	131	152	180	618	21	23	24	5	1	74	692
Number becoming positive to tuberculin during training . . . . .	30	39	45	57	44	215	10	8	6	2	1	27	242
Percentage becoming positive to tuberculin during training . . . . .	48.4	41.9	34.4	37.5	24.4	34.8	47.6	34.8	25.0	40.0	100.0	36.5	35.0
<b>Winnipeg General Hospital:</b>													
Number negative to tuberculin on entrance . . . . .	46	54	35	41	50	226	59	53	53	60	82	307	533
Number becoming positive to tuberculin during training . . . . .	26	31	15	21	25	118	27	16	13	14	9	79	197
Percentage becoming positive to tuberculin during training . . . . .	56.5	57.4	42.9	51.2	50.0	52.2	45.7	30.2	24.5	23.3	11.0	26.0	37.0

*Infection rate of non-vaccinated negatives year by year during training in eight Saskatchewan Hospitals*

Based on remainders

YEAR OF ENTERING TRAINING . . . . .	1934	1935	1936	1937	1938	1934-1938	1939	1940	1941	1942	1943	1939-1943	1934-1943
Number negative to tuberculin on entrance . . . . .	62	93	131	152	180	618	21	23	24	5	1	74	692
Number becoming positive to tuberculin in first year of training . . . . .	7	10	16	7	22	62	9	3	5	1	—	18	80
Per cent becoming positive to tuberculin in first year of training . . . . .	11.3	10.75	12.2	4.6	12.2	10.0	42.9	13.0	20.8	20.0	—	24.3	11.5
Number remaining negative after first year's exposure . . . . .	55	83	115	145	158	556	12	20	19	4	1	56	612
Number becoming positive to tuberculin in second year of training . . . . .	6	9	13	27	17	72	1	3	—	1	1	6	78
Per cent becoming positive to tuberculin in second year of training . . . . .	10.9	10.8	11.3	18.6	10.76	12.95	8.3	15.0	—	25.0	100.0	10.7	12.7
Number remaining negative after two years' exposure . . . . .	49	74	102	118	141	484	11	17	19	3	—	50	534
Number becoming positive to tuberculin in third year of training . . . . .	10	8	11	23	5	57	—	2	1	—	—	3	60
Per cent becoming positive to tuberculin in third year of training . . . . .	20.4	10.8	10.8	19.5	3.55	11.8	—	11.8	5.3	—	—	6.0	11.2
Number remaining negative after three years' exposure . . . . .	39	66	91	95	136	427	11	15	18	3	—	47	474
Number requiring over three years to become positive to tuberculin . . . . .	7	12	8	—	—	24	—	—	—	—	—	—	24
Per cent requiring over three years to become positive to tuberculin . . . . .	17.9	18.2	5.49	—	—	5.62	—	—	—	—	—	—	5.1

The unusual significance of this study arises from the fact that all were females; the age of both vaccinated and non-vaccinated is considered a susceptible period,

being age 20; the infectivity of the environment and period of exposure in the environment, probably the two most fundamental factors, are very comparable. There was no evidence that contact with tuberculosis prior to entering training was a significant factor.

The infectivity of the environment as shown by the non-vaccinated negatives has been relatively stable during the entire period (see table 2). The year by year incidence of infection throughout the three years of training remained quite comparable for each class that entered training, being 11.5, 12.7 and 11.2 per cent, respectively, for the first, second and third year of training. The probable sources of infection are indicated by the record of the number of patient-days for

TABLE 3

*Showing known sources of infection in eight Saskatchewan Hospitals*

This table shows days of treatment for tuberculosis paid for by the League in the eight Hospitals studied. Also shown are the average number of tuberculous patients in these hospitals, as well as the white death-rate from tuberculosis in Saskatchewan for the period studied.

YEAR	AVERAGE NUMBER OF TUBERCULOSIS PATIENTS	TREATMENT DAYS FOR TUBERCULOSIS IN EIGHT HOSPITALS STUDIED	WHITE TUBERCULOSIS DEATH-RATE PER 100,000 POPULATION
1934	38	13,836	23.0
1935	25	9,263	22.7
1936	33	11,996	22.2
1937	16	5,807	22.2
1938	22	8,156	19.2
1939	38	13,828	16.2
1940	32	11,496	17.1
1941	42	15,501	20.2
1942	48	17,428	16.8
1943	32	11,619	21.0
1944	55	20,091	17.2

Although there has been fluctuation in treatment days for tuberculosis patients in the tuberculosis wards maintained in the eight Saskatchewan Hospitals during the period studied, they have been relatively constant with the exception of the years 1935, 1937 and 1938. As will be noted from table 2, the incidence of infection during the entire period has been relatively constant.

the treatment of tuberculosis in these eight hospitals (see table 3). (These eight hospitals have been used as overflow accommodation for the treatment of tuberculosis throughout the period.) All treatment for tuberculosis being free to the sick in Saskatchewan and paid for by the League, it is assumed that this is a fair index.

The average periods of exposure to the environment of all groups are relatively quite comparable, being 2.42 years, 2.54 years and 2.47 years, for the vaccinated, non-vaccinated negatives and positive groups, respectively.

The general conditions of the environments studied have been quite stable. Matters of food, working and living conditions to which the exposed persons have

TABLE 4A

*Type of disease of cases of tuberculosis in hospital study only*  
Eight Saskatchewan Hospitals

	VACCINATED GROUP	NEGATIVE GROUP	POSITIVE GROUP	TOTAL CASES
Pulmonary tuberculosis — parenchymal .....	5 (2)	11 (2)	3	19 (4)
Pulmonary tuberculosis — complicated by cervical adenitis .....	—	1	—	1
Pulmonary tuberculosis—progressing to contralateral lung and spine .....	—	1	—	1
Pleurisy with effusion only .....	3	7	—	10
Pleurisy with effusion progressing to parenchymal disease .....	—	3	—	3
Erythema nodosum only .....	1 (1)	2 (2)	—	3 (3)
Erythema nodosum progressing to pleurisy with effusion .....	—	3	—	3
Erythema nodosum progressing to parenchymal disease .....	—	1 (1)	—	1 (1)
Total cases of tuberculosis .....	9 (3)	29 (5)	3 (0)	41 (8)

*Note:* Figures in brackets denote cases *not treated*, that is, of the 9 cases of tuberculosis in the vaccinated group, 3 were not treated.

TABLE 4B

*Type of disease of cases of tuberculosis in Saskatchewan Sanatoria study only*

	VACCINATED GROUP	NEGATIVE GROUP	POSITIVE GROUP	TOTAL CASES
Pulmonary tuberculosis — parenchymal .....	4 (2)	20 (7)	9 (6)	33 (15)
Pulmonary tuberculosis progressing to miliary tuberculosis and death .....	—	1	—	1
Pulmonary tuberculosis progressing to tuberculous ankle .....	—	1	—	1
Pleurisy with effusion only .....	4	4	—	8
Pleurisy with effusion progressing to parenchymal disease .....	—	1	—	1
Pleurisy without effusion .....	—	1	—	1
Erythema nodosum only .....	1	3 (1)	2	6 (1)
Erythema nodosum progressing to pulmonary tuberculosis .....	—	1	—	1
Cervical adenitis only .....	—	—	1 (1)	1 (1)
Renal tuberculosis .....	—	—	1	1
Total cases of tuberculosis .....	9 (2)	32 (8)	13 (7)	54 (17)

*Note:* Figures in brackets denote cases *not treated* in each group.

been subjected have not varied appreciably throughout the period of time covered by the studies.

It would seem from the above that known factors, other than vaccination, which might influence the cases in regard to developing disease are comparable.

There were 2,042 cases accepted for study (see table 1).

*Findings:* Among 1,005 vaccinated cases there were 9 who developed manifest tuberculosis, or 0.895 per cent (the term manifest tuberculosis used throughout this study means pulmonary tuberculosis demonstrable by X-ray, and nonpulmonary cases of tuberculosis as seen in table 4); among 759 negative non-vaccinated cases there were 29 who developed manifest tuberculosis, or 3.82 per cent; among 278 cases positive to tuberculin on entrance, there were 3 who developed manifest tuberculosis, or 1.08 per cent.

The difference in percentages between the vaccinated and the non-vaccinated negatives is 2.925 per cent, which is 5.8 times its own probable error, and therefore of statistical significance. The ratio is 1:4.27.

#### EXPERIENCE IN THE WINNIPEG GENERAL HOSPITAL, WINNIPEG, MANITOBA

BCG vaccination was not carried on in the Winnipeg General Hospital, and nurses entering training in this hospital during the period of 1934 to 1943, inclusive, were studied as a comparable non-vaccinated negative group for the above Saskatchewan study.

Since 1937 the hospital has discontinued the custom of sending nurses, negative to tuberculin, to the King Edward Sanatorium for affiliate training in tuberculosis nursing. Since 1939 the hospital has practiced increased segregation in regard to tuberculosis—the Central Tuberculosis Clinic has been called on for consultation whenever a patient admitted to the hospital was suspected of having tuberculosis. If on examination the patient was found to be tuberculous he was immediately removed to the wards of the tuberculosis clinic. This segregation has had the effect of reducing appreciably the infectivity of the environment. In the classes entering since 1940 the infectivity has fallen from an average of about 50 per cent infected during training in the preceding classes to an average of 25 per cent infected during training. However, the average infectivity for the ten-year period 1934–1943 in both the Winnipeg General Hospital and the Saskatchewan Hospitals has been very comparable (see table 2); 37 per cent of the negative non-vaccinated became infected during training in the Winnipeg General Hospital, and 35 per cent of the negative non-vaccinated became infected during training in the Saskatchewan Hospitals. The average period of exposure to the environment of the negative and positive reactors was 2.28 years and 2.39 years, respectively, which closely approximates the average period of exposure in the Saskatchewan Hospital study. The general living conditions were found to be comparable with the Saskatchewan group. Average age on entrance was the same, being 20 years.

There were 809 cases accepted for study (see table 1).

*Findings:* Among 609 non-vaccinated negatives in the Winnipeg General 26 developed manifest tuberculosis, or 4.26 per cent; among 200 positive reactors



2 developed manifest tuberculosis, or 1 per cent. Taking the Winnipeg General Hospital non-vaccinated negatives as a comparable group for the Saskatchewan vaccinated group, we find the difference in percentages is 3.365 per cent, which is 5.7 times its own probable error. The ratio is 1:4.8.

Combining both the Saskatchewan Hospital study and the Winnipeg General Hospital study for the purpose of comparing larger numbers, we find that the resultant average time of exposure to the environments for the vaccinated, non-vaccinated negatives, and positive groups is 2.426 years, 2.437 years and 2.43 years, respectively. Among 1,005 vaccinated cases there were 9 who developed manifest tuberculosis, or 0.895 per cent; among 1,368 non-vaccinated negatives there were 55 who developed manifest tuberculosis, or 4.02 per cent; among 478 positives there were 5 who developed manifest tuberculosis, or 1.046 per cent. The difference in percentages in comparing the vaccinated with the non-vaccinated negatives is 3.125 per cent, which is 7.6 times its own probable error. The ratio is 1:4.5.

It would seem, then, that the use of BCG vaccination in the hospital environment has reduced manifest tuberculosis among negative reactors to its fourth. Of the 9 cases of manifest tuberculosis in the vaccinated group, only 66.6 per cent required treatment while, in the 55 cases of manifest tuberculosis in the non-vaccinated negative group, 82.8 per cent required treatment.

An interesting observation regarding the developing of manifest tuberculosis among the negative non-vaccinated group is that roughly 80 per cent of the cases developing tuberculosis did so within a year of becoming infected.

There were no deaths from tuberculosis in any of these groups.

#### EXPERIENCE IN THREE SANATORIA IN SASKATCHEWAN

The groups studied in the sanatoria were the vaccinated and non-vaccinated negatives and positives under the following occupations: graduate nurses, nurses' assistants, kitchen maids, orderlies and a miscellaneous group comprised of laundry staff, laboratory staff, X-ray staff and house maids, all of whom had a rate of infection higher than that experienced in the hospital environments studied above.

The first three occupational groups are of the female sex and of an average age of 23.3 years on entrance. The occupational groups, orderlies and miscellaneous, comprise both males and females and their average age is 24.3 years on entrance.

General conditions in the sanatoria environment have remained much the same; matters of food, working hours and living conditions to which the exposed persons have been subjected have not varied appreciably throughout the period covered. All employes entering the environment during the period 1934 to 1943, inclusive, were considered; there were 1,206 accepted for study (see table 5).

The infectivity of the environment has remained high throughout the period of study, as would be expected. The incidence of infection among the non-vaccinated negatives remained reasonably stable, being 74.2 per cent in the

TABLE 5

*BCG vaccination among exposed employees in Saskatchewan Sanatoria*

Showing percentage developing manifest tuberculosis in each occupational group studied  
 Employees entering sanatorium environment—period 1934-1943

ACCEPTED FOR STUDY	NUMBER OF PERSONS	TUBERCULOSIS CASES	PER CENT WITH TUBERCULOSIS	PROBABLE ERROR	YEARS OBSERVED	AVERAGE YEARS OBSERVED
<b>BCG vaccinated employees:</b>						
Nurses' assistants.....	143	4	2.8		163.48	1.14
Graduate nurses.....	60	1	1.67		54.78	0.925
Kitchen and diet kitchen maids	140	2	1.43		195.59	1.4
Orderlies and cleaners.....	69	1	1.45		70.28	1.02
Miscellaneous group.....	58	1	1.72		73.70	1.27
Total vaccinated.....	470	9	1.92	±0.42	557.83	1.19
Graduate nurses and nurses' assistants combined.....	203	5	2.46	±0.74	218.26	1.075
<b>Negative to tuberculin on entrance—non-vaccinated:</b>						
Nurses' assistants.....	54	10	18.5		74.15	1.37
Graduate nurses.....	59	8	13.54		45.68	0.774
Kitchen and diet kitchen maids	82	7	8.54		158.13	1.93
Orderlies and cleaners.....	38	4	10.5		54.33	1.43
Miscellaneous group.....	41	3	7.32		62.86	1.53
Total negatives non-vaccinated.....	274	32	11.67	±1.31	395.15	1.44
Graduate nurses and nurses' assistants combined.....	113	18	15.9	±2.32	119.83	1.06
<b>Positive to tuberculin on entrance:</b>						
Nurses' assistants.....	99	4	4.04		135.28	1.37
Graduate nurses.....	194	7	3.61		232.94	1.2
Kitchen and diet kitchen maids	74	1	1.35		110.49	1.5
Orderlies and cleaners.....	60	—	—		130.41	2.17
Miscellaneous group.....	35	1	2.86		56.57	1.61
Total positives.....	462	13	2.81	±0.52	665.69	1.44
Graduate nurses and nurses' assistants combined.....	293	11	3.75	±0.74	368.22	1.25
<b>Total:</b>						
Nurses' assistants.....	296	18	6.08		372.91	1.26
Graduate nurses.....	313	16	5.1		333.40	1.06
Kitchen and diet kitchen maids	296	10	3.4		464.21	1.57
Orderlies and cleaners.....	167	5	3.0		255.02	1.52
Miscellaneous group.....	134	5	3.73		193.14	1.44
Total accepted for study.....	1,206	54	4.47	—		

period 1934-1938 and 70.3 per cent in the period 1939-1943. The probable sources of infection are indicated in table 6, which shows the number of cases year by year with positive sputum who were treated in the sanatoria.

The average time of exposure for the various groups, vaccinated, non-vaccinated negatives, and positives, was 1.19 years, 1.44 years and 1.45 years, respectively; the time factor is not entirely comparable, the vaccinated group having on the average three months less exposure to the environment than either the non-vaccinated negatives or positive groups.

The rate of infection in the sanatoria environment for the first year of exposure as shown in table 7 is 60 per cent. This rate appeared high, so it was checked with that obtaining in the Manitoba Sanatorium and the St. Boniface Sanatorium and was found to be comparable.

TABLE 6

*Showing sources of infection in Saskatchewan Sanatoria*  
Proportion of adult pulmonary cases with positive sputum in three Saskatchewan Sanatoria  
—as of December 31st of each year

YEAR	TOTAL CASES	INFECTIOUS CASES	PERCENTAGE INFECTIOUS
1934	504	422	83.7
1935	499	425	85.1
1936	516	455	88.1
1937	546	472	86.5
1938	562	456	81.1
1939	569	455	79.9
1940	587	449	76.5
1941	610	443	72.6
1942	550	435	79.1
1943	582	425	73.0
1944	593	471	79.3

This table is an indication of the relative constancy of sanatorium environment under consideration during the period of this study. It will be noted that, although the percentages of positive sputum cases varies downward to some extent, the actual number of infectious cases remains relatively constant throughout the ten-year period.

Vaccination in such an environment will be put to a severe test and the findings regarding the efficacy of vaccination under these conditions should have considerable weight.

*Findings:* Among 470 vaccinated cases in the occupational groups mentioned previously, 9 developed manifest tuberculosis, or 1.92 per cent. We attempted to correct the time factor among the vaccinated persons, assuming that the cases developing manifest tuberculosis in the additional three months' exposure (which will make the average time for the vaccinated entirely comparable with the non-vaccinated negatives and the positives, that is, 1.44 years) will do so at the same rate obtaining during the actual time exposed, 1.19 years. This calculation to equalize the time factor results in the following: among 470 vaccinated cases in the occupational groups mentioned previously, 2.32 per cent developed mani-

TABLE 7

*Incidence of infection of non-vaccinated negatives in Saskatchewan Sanatoria*  
 Showing percentages infected in three-month periods—based on remainders  
 (Using only those negatives who had satisfactory tuberculin information)

	3 MOS.	6 MOS.	9 MOS.	12 MOS.	15 MOS.	18 MOS.	24 MOS.	30 MOS.	30+ MOS.	TOTAL
<b>Nurses' assistants</b>										
Total negative.....	47	39	22	14	12	10	8	6	6	47
Number infected.....	8	17	8	2	2	2	2	—	—	41
Per cent infected.....	17.0	43.5	36.3	14.3	16.6	20.0	25.0	—	—	87.2
Cumulative number infected.....	8	25	33	35	37	39	41	41	41	41
Cumulative per cent infected.....	17.0	53.2	70.2	74.5	78.7	83.0	87.2	87.2	87.2	87.2
<b>Graduate Nurses</b>										
Total negative.....	45	40	22	15	14	14	14	14	13	45
Number infected.....	5	18	7	1	—	—	—	1	—	32
Per cent infected.....	11.1	45.0	31.8	6.67	—	—	—	7.15	—	71.1
Cumulative number infected.....	5	23	30	31	31	31	31	32	32	32
Cumulative per cent infected.....	11.1	51.1	66.7	69.0	69.0	69.0	69.0	71.1	71.1	71.1
<b>Kitchen and Diet Kitchen Maids</b>										
Total negative.....	66	57	51	42	35	27	22	20	19	66
Number infected.....	9	6	9	7	8	5	2	1	1	48
Per cent infected.....	13.6	10.5	17.6	16.6	22.8	18.5	9.1	5.0	5.26	72.7
Cumulative number infected.....	9	15	24	31	39	44	46	47	48	48
Cumulative per cent infected.....	13.6	22.7	36.4	47.0	59.0	66.7	69.7	71.2	72.7	72.7
<b>Orderlies and Cleaners</b>										
Total negative.....	31	23	11	10	7	7	5	3	3	31
Number infected.....	8	12	1	3	—	2	2	—	—	28
Per cent infected.....	25.8	52.2	9.1	30.0	—	28.6	40.0	—	—	90.3
Cumulative number infected.....	8	20	21	24	24	26	28	28	28	28
Cumulative per cent infected.....	25.8	64.5	67.7	77.4	77.4	84.0	90.3	90.3	90.3	90.3
<b>Miscellaneous</b>										
Total negative.....	34	32	29	24	21	21	20	20	20	34
Number infected.....	2	3	5	3	—	1	—	—	1	15
Per cent infected.....	5.88	9.38	17.2	12.5	—	4.76	—	—	5.0	44.1

TABLE 7—Continued

	3 MOS.	6 MOS.	9 MOS.	12 MOS.	15 MOS.	18 MOS.	21 MOS.	24 MOS.	30+ MOS.	TOTAL
Cumulative number infected.....	2	5	10	13	13	14	14	14	15	15
Cumulative per cent infected.....	5.88	14.7	29.4	38.2	38.2	41.2	41.2	41.2	44.1	44.1
Total										
Total negative.....	223	180	132	105	89	79	69	63	61	223
Number infected.....	43	48	27	16	10	10	6	2	2	164
Per cent infected.....	19.3	26.7	20.4	15.2	11.2	12.7	8.7	3.17	3.28	73.5
Cumulative number infected.....	43	91	118	134	144	154	160	162	164	164
Cumulative per cent infected.....	19.3	40.8	52.0	60.0	64.5	69.0	71.7	72.6	73.5	73.5

fest tuberculosis. Among 274 non-vaccinated negatives in the occupational groups mentioned above, 32 developed manifest tuberculosis, or 11.67 per cent. Among 462 positives in the same occupational groups, 13 developed manifest tuberculosis, or 2.81 per cent. The difference in percentages between the vaccinated and non-vaccinated negative groups (using the calculated figure for the vaccinated group) is 9.35 per cent, which is 6.7 times its own probable error. The ratio is 1:5.03.

There was one death from tuberculosis in this Sanatoria study, which occurred in the non-vaccinated negative group.

#### EXPERIENCE OF GRADUATE NURSES AND NURSES' ASSISTANTS SELECTED FROM THE SANATORIA STUDY BECAUSE THEY WERE SUBJECTED TO THE STRAIN OF MORE EXCESSIVE INFECTION

Combining the experience of the graduate nurses and nurses' assistants who have much the same type of exposure to the environment, are of the same sex and in the same age-group (25.5 years and 22.7 years, respectively), we find that the period of exposure for the vaccinated and non-vaccinated negatives and positives is 1.075 years, 1.06 years and 1.255 years, respectively (see table 5).

The incidence of infection in the nurses' group was 71.8 per cent after one year's exposure; this is practically the same rate obtaining in the Manitoba Sanatorium and St. Boniface Sanatorium where the incidence of infection for these groups after one year's exposure was 71.5 per cent and 79.7 per cent, respectively, during the same period.

*Findings:* Among 203 vaccinated nurses, 5 developed manifest tuberculosis, or 2.45 per cent; among 113 non-vaccinated negative nurses, 18 developed manifest tuberculosis, or 15.9 per cent; among 293 nurses positive to tuberculin, 11 developed manifest tuberculosis, or 3.75 per cent. The difference in percentages between the vaccinated nurses and non-vaccinated negative nurses is 13.44 per

cent, which is 5.5 times its own probable error and therefore of statistical significance. The ratio is 1:6.5.

It has been pointed out that vaccination as carried on in this study was instituted after the negative reactor entered the infectious environment and while on duty. The method is practical and can be carried out without inconvenience. It is realized, however, that in environments where the incidence of infection is 1 per cent per month (Saskatchewan Hospital environment) and 5 per cent per month (Saskatchewan Sanatoria environment) some persons become infected before vaccination is effective. This constitutes a slight weighting against the vaccinated group.

#### CONCLUSIONS

1. BCG vaccination of nurses negative to tuberculin on entrance to a General Hospital environment, where the rate of infection was approximately 12 per cent *per annum* among the non-vaccinated negatives, and the duration of exposure was 2.42 years, reduced the number of cases of manifest tuberculosis that developed among this group to its fourth; the ratio of vaccinated negatives as compared with non-vaccinated negatives is 1:4.27.

2. BCG vaccination of Saskatchewan Sanatoria employees negative to tuberculin on entrance to the sanatorium environment, where the rate of infection among the non-vaccinated negatives was 60 per cent during the first year of exposure, and the duration of exposure was 1.44 years, reduced the number of cases of manifest tuberculosis that developed among this group to its fifth; the ratio of vaccinated negatives as compared with non-vaccinated negatives is 1:5.03.

3. These findings are of statistical significance.

4. BCG is not a 100 per cent effective prophylactic; its protection is very considerable, but by no means absolute.

5. BCG vaccination was found to be safe.

6. Regarding the severity of manifest tuberculosis developed among the vaccinated as compared with the non-vaccinated negatives, it was found that in the vaccinated group the lesions were less extensive.

7. The serious situation that had been developing with regard to excessive incidence of tuberculosis among nurses and sanatoria employees who did not react to tuberculin on entering the environment, during the period 1930 to 1938, has not been present since vaccination of negative reactors was begun in September, 1938. The nursing schools and the League in Saskatchewan no longer have anxiety and worry with regard to excessive tuberculosis developing among their negatively reacting staff.

#### CONCLUSIONES

1. La vacunación con BCG de las enfermeras tuberculino-negativas a su entrada en un medio de Hospital General, en el cual el coeficiente de infección era aproximadamente de 12 por ciento al año en las negativas no vacunadas y

la exposición promediaba 2.42 años, hizo bajar a la cuarta parte el número de casos de tuberculosis declarada en el grupo; la proporción de negativas en las vacunadas comparadas con las no vacunadas es de 1:4.27.

2. En los sanatorios de Saskatchewan la vacunación con BCG, a su entrada, de los empleados negativos a la tuberculina, entre los que el coeficiente de infección en los negativos no vacunados había sido de 60 por ciento durante el primer año de exposición, y la exposición durado 1.44 años, hizo bajar a la quinta parte el número de casos de tuberculosis manifiesta en el grupo, mientras que la proporción de negativos en los vacunados y los no vacunados es de 1:5.03.

3. Estos hallazgos poseen importancia estadística.

4. BCG, como profiláctico, no es 100 por ciento eficaz; su valor protector es muy considerable, pero no absoluto en modo alguno.

5. La vacunación con BCG resultó inocua.

6. En cuanto a la gravedad de la tuberculosis manifiesta observada en los negativos vacunados en comparación con los no vacunados, en los primeros las lesiones resultaron ser menos extensas.

7. El grave problema que iba planteando la excesiva incidencia de la tuberculosis en las enfermeras y empleados de los sanatorios que no reaccionaban a la tuberculina al ingresar en dicho medio, durante el período 1930-1938, ha desaparecido desde que se inició la vacunación de los reactivos negativos en septiembre, 1938. Las escuelas de enfermería y la Liga Antituberculosa de Saskatchewan no tienen ya porqué preocuparse y mostrarse ansiosas acerca de la excesiva tuberculosis mostrada por el personal que reacciona negativamente a la tuberculina.

#### *Acknowledgments*

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Valuable assistance was also contributed by the Superintendents of Nurses in the Sanatoria and General Hospitals of Saskatchewan. It is also desired to acknowledge the assistance of the Radiologists of the General Hospitals throughout this study.

Sincerest appreciation is due Dr. Armand Frappier, of the Institute of Microbiology and Hygiene of the University of Montreal, for his assistance in supplying the vaccine for this study. Appreciation is also due Dr. D. L. Scott, of the Central Tuberculosis Clinic, Sanatorium Board of Manitoba, for his medical services in connection with the study in the Winnipeg General Hospital.

Special mention should be made of the work done by Miss Jeannette Broderick, Mr. K. B. Gillie and Mr. Frank Froh who enthusiastically pursued the tedious statistical and clerical work connected with this study.

#### REFERENCE

- (1) KERESZTURI, CAMILLE, AND PARK, WILLIAM H.: The use of the BCG vaccine against tuberculosis in children, *Am. Rev. Tuberc.*, 1936, 34, 437.

## DISCUSSION

*Dr. Joseph D. Aronson, Philadelphia, Pennsylvania:* Dr. Ferguson's studies under controlled conditions show a definite decrease in the incidence of tuberculosis among nurses in training, and nurses and attendants of sanatoria who have been vaccinated with BCG vaccine. We should like, at this time, to present corroborative evidence as a result of a controlled study to determine the value of BCG among Indians in the United States and Alaska. This study had its inception in 1935 as a cooperative investigation by the Office of Indian Affairs and the Henry Phipps Institute of the University of Pennsylvania, and, more recently, the Tuberculosis Control Division, U. S. Public Health Service and the National Tuberculosis Association.

From February, 1936 to February, 1938 1,550 persons, ranging in age from less than one year to 19 years of age, were vaccinated intracutaneously with either 0.1 or 0.15 mg. of freshly prepared BCG vaccine. During this same period 1,457 persons of the same age and sex, living in the same areas and under the same conditions, received 0.1 cc. of sterile physiological salt solution and served as controls.

All persons included in this study failed to react initially to 0.000,02 and 0.005 mg. of PPD tuberculin, and, with few exceptions, the chests of the two groups were X-rayed either before or shortly after they were included in this study. Tuberculin tests and X-ray films were made annually of both groups. The tuberculin tests were given and interpreted by the same person, while the X-ray films were originally read by a member of the study group, without his knowing whether the film was from a vaccinated or control case. Subsequently all films were reviewed by a roentgenologist of the Tuberculosis Control Division of the U. S. Public Health Service, who had no connection with the original study.

A history of exposure to tuberculosis was found in 21.4 per cent of the vaccinated, and in 19.8 per cent of the controls. During the first five years of this study approximately 90 per cent of both groups were reexamined annually, while during the sixth year, due to the war, only about 75 per cent were reexamined. Among the controls, a total of 60 deaths from all causes has occurred during the six years of observation, as compared with 34 deaths in the BCG vaccinated group. Of the 60 deaths among the controls, 28 were due to tuberculosis, while among the BCG group only 4 of the 34 deaths were due to this disease. The total number of cases of tuberculosis, including deaths from this disease, was 40 in the BCG group and 185 among the controls. Of special significance is the life table experience of the two groups during the six years of observation. Thus the attack rate per thousand person-years of exposure for the BCG cases was 11.8, 6, 2, 4.1, 2.2 and 0.8, respectively, while for the control group it was 26.1, 23.3, 23.3, 26.1, 21.9 and 25, respectively. Of interest is the high incidence of tuberculosis during the first two years following vaccination, after which the rates per thousand years of exposure declined rapidly. On the other hand, among the control group the rates during the six years of observation remained approximately the same. The 4 deaths among the BCG vaccinated group occurred within the first 2 years following vaccination. Among the control group deaths from tuberculosis have occurred in all of the years of the study.

Our results indicate objectively that BCG vaccination is associated with definite protection against the development of tuberculosis, as measured by the mortality and morbidity experience of the two groups included in this study. The results of this study lend support to the use of the BCG vaccine as a protective measure for tuberculin-negative persons who, either because of their duties, social or economic conditions, may be exposed to tuberculosis.



# THE PSYCHOLOGICAL MOMENT IN THE TREATMENT OF TUBERCULOSIS

J. D. RILEY<sup>1</sup>

Constantly growing importance is being attached to preventive medicine. Likewise there is wider recognition of emotional problems in illness. These considerations emphasize that the modern medical man must cherish and play the rôle which his title of honor—"doctor"—implies is still his. For "doctor" originally meant "teacher."

This is no new responsibility for physicians. It is, however, an aspect of the art which many have been inclined to overlook during a period when astonishing scientific discoveries have dominated the medical scene. The contributions which chemistry, physics and biology have made to medical science are in no way diminished by the admission that these are contributory to medicine as an art, but that they do not comprise the whole of medicine. The physician deals, first and last, with something more than a collection of organs in varying degrees of dysfunction. He is concerned with a human being.

This human being who comes with his questions or his needs to the physician requires, first of all, a diagnosis—that is, a recognition and an evaluation of his physical state. Diagnosis may present no problem if symptoms are clear-cut or altogether absent. At times, however, it can be given only after an exhaustive exploration with the best laboratory and technical tools available. But in this case, even as the symptoms are being elicited, the true physician is already probing for the facts and making the observations which will guide him in the next and perhaps the most important portion of his total service to the patient—that of acquainting him with the true state of affairs and preparing him for treatment when necessary. It is, then, that the doctor functions primarily as a teacher, a friend, and only secondarily as a man of science. It is at this time that he may utilize to advantage the principles and practices of education.

"There is a tide in the affairs of men which taken at the flood leads on . . .," says the poet. "There is also a tide in the educational life of a child or of an adult," says one educator. This is "when one is in a position to learn efficiently and rapidly. Leaders watch for these *teachable moments* and utilize them to their fullest." The teachable moment is more often called the psychological moment, a term full of meaning to any thoughtful person.

The time at which the physician acquaints the patient with his diagnosis, especially when it is that of a chronic disease such as tuberculosis, is such a moment. It is then that the fearful patient, with every sense quickened, listens with all his being in order that no word of the physician, no implication of his tone or manner will escape notice or be given less than its true importance. It is often, at this time, that the foundation is laid for a successful recovery from tuberculosis. Sometimes, unfortunately, the golden opportunity is wasted, with disastrous and disappointing consequences.

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To assemble the facts, to weigh the possibilities, to help the patient face the reality and to be ready with constructive plans, calls for great skill on the part of the physician. He must make sure that the implications of the diagnosis are understood, yet he must be as optimistic as the facts warrant if his patient is to undertake treatment hopefully. He must stress the necessity for a drastic change in the life and plans of the patient, yet never proceed faster than the patient is ready to go along with him in his thinking. If handled hurriedly or casually, the patient may refuse to accept the diagnosis; he may delay or postpone treatment; or he may undertake his cure in so rebellious or apathetic a spirit that he nullifies the best efforts of the hospital and medical staff. The difference between what should happen and what does happen to an individual tuberculosis patient is often determined by the attitudes and teaching of the physician who first makes the diagnosis. This is the time when treatment really begins. In tuberculosis the sequence of diagnosis, treatment and rehabilitation should always overlap and be woven together as a well-spliced rope, strong enough to haul the patient from danger back to safety.

What is the duty of the physician to the man or woman on whom he makes a diagnosis of pulmonary tuberculosis?

First of all, he should come to a tentative decision after he completes the examination and before he notifies the patient. A diagnosis of tuberculosis does not have a definite meaning. It varies all the way from an arrested case needing supervision but no treatment to the clinically active, open, incurable case. What the physician's duty is depends on his findings in the individual case. If the patient has active tuberculosis, it should be discussed and handled as a communicable disease.

With full consideration for the patient's intelligence and temperament, without equivocation or mental reservation, the physician should tell the patient, preferably in the presence of a responsible relative, that he has tuberculosis and he should explain the case frankly. He should not overestimate nor underestimate; he should give the patient the facts as he sees them.

It is quite possible, by properly taken stereoscopic pictures, to determine almost exactly how much tuberculosis the patient has. It is quite impossible by X-ray pictures alone to establish the degree of clinical activity, perhaps the most important aspect of the prognosis. The patient should be told that only after a consideration of clinical and laboratory findings, of constitutional symptoms and of his response to treatment, as shown by X-ray films, can any estimate of the progressiveness of the disease or the length of time required for treatment be made.

It is not usually possible for the physician who makes the diagnosis to educate the patient in matters of tuberculosis—time will not permit. He should, however, never dismiss the patient without making sure that he has accepted the necessity for treatment. At this point, the physician might well remember that there is a time element in the learning process. It is inevitable that there will be some shock when a patient is told that he has tuberculosis and is in need of hospital treatment. No attempt, therefore, should be made to hurry practical

arrangements until the patient indicates by his question them. An emotional acceptance of these two basic facts of tuberculosis and that treatment is essential, is fundamental. Once acceptance is obtained, progress along other lines should not be delayed.

This may take time, and perhaps the help of the public health social worker will be needed before the patient and his family are ready with plans for treatment. Perhaps a confirmatory diagnostic specialist will be required. But until plans are completely initiated the patient is still under the care of the physician. The responsibility for sound and careful guidance of the patient, the family and for interim treatment rests with him.

I do not believe in compulsion. If we could compel every patient to the cure until his disease was arrested, we could not then consider his limitations in order to avoid further breakdowns. Patients must take the cure. They must be so anxious to get well that they will accept the restrictions and limitations necessary for their recovery.

Once the patient is in the sanatorium, he becomes the responsibility of the sanatorium physician. Immediately upon admission the physician should explain to the patient that the treatment of tuberculosis is educational. First, it is necessary for every patient to be educated about tuberculosis.

Intelligence is the most potent factor that can be directed toward the cure. No question asked by an earnest patient is too insignificant. Every fact that will aid him in recovering health should be withheld.

The physician who treats tuberculosis naturally becomes a teacher and instructor in health problems. He should stress the importance of his disease under control and of practicing sanitary precautions. He should not menace the health of his relatives, friends and others. He should tell the patient that he must learn his limitations, and how to live with them not only in the sanatorium but after he leaves it.

If the patient understands the character of the disease and its treatment, he will know why it is necessary for him to follow closely a doctor's instructions, to give up seemingly harmless pleasures and avoiding undue activity in the home and social world. It is all but impossible to secure coöperation if the patient does not understand the reason for it. It is an insult to his intelligence to tell him to rest in bed, to give up business and to follow such instructions if he has no definite idea of the reason. In the treatment of tuberculosis if he has no definite idea of the reason, he will not cooperate. Since there are excellent reasons for each of these steps, they should be explained and fully accepted.

An understanding of the tuberculosis hospital will help the patient in preparing his patient for treatment there. It will also encourage the patient to accept effective counsel when the patient returns from the hospital.

The patient whose coöperation is enlisted at the time of the diagnosis is apt to become a good patient while in the tuberculosis hospital. Moreover, it is a common observation that such patients not only do better under treatment but are more successful in staying well after they leave the sanatorium.

Spectacular results in reducing the death rate from tuberculosis have been achieved in the past few decades. We are now reaching the point of diminishing returns unless the physician in general practice concerns himself more than ever before in getting under treatment all active cases promptly after they are discovered. To do this he must seize the opportunity which comes to him when he tells the patient of the diagnosis. Here is a teachable moment. The entire future course of his patient's life may be determined in the short course of the half-hour the doctor has at his disposal. Here may be laid the foundation for an interested, intelligent and hopeful approach to the curing of the disease which endangers the patient, his family and the community. On the other hand, here also may be the tide which "omitted, all the voyage . . . is bound in shallows and in miseries." The physician who understands the meaning of teachable moments in tuberculosis will not fail to take advantage of this opportunity which will come but once with every patient. The foundation for successful treatment in tuberculosis is laid when the doctor tells the patient that he has the disease. Psychologically, medically and economically, this may well prove to be the biggest moment in the patient's life.

#### SUMMARY

1. In tuberculosis, the physician who makes the diagnosis has a unique opportunity to lay the foundation for successful treatment of the patient.

2. The time at which a patient is told that he has tuberculosis needing treatment is the psychological or teaching moment for establishing a constructive attitude in the patient toward his disease and the tuberculosis hospital.

3. Such an attitude gives the patient the greatest chance for recovery from tuberculosis and lessens the possibility of recurrence.

4. If the patient is not prepared for treatment at the time of diagnosis, the opportunity for doing so easily is lost.

#### SUMARIO

1. En la tuberculosis, el médico que hace el diagnóstico tiene una oportunidad única de establecer la base para el tratamiento con éxito del enfermo.

2. El momento en que se le dice al enfermo que tiene tuberculosis y que necesita tratamiento también es el momento psicológico o didáctico para crear una actitud propicia de parte del enfermo hacia su enfermedad y hacia el hospital de tuberculosos.

3. Esa actitud de parte del enfermo le proporciona las mayores probabilidades de curación y merma la posibilidad de recurrencias.

4. Si al hacer el diagnóstico no se prepara al enfermo para tratamiento, se pierde fácilmente la oportunidad de hacerlo.

## THE IMPORTANCE OF POSTSANATORIUM CARE OF THE TUBERCULOUS

FRED H. HEISE<sup>1</sup>

Pulmonary tuberculosis at best is a disease of many years of uncertain course which frequently is marked by periods of an apparently healed condition and periods of reactivation. It is true that many individuals recover spontaneously, never knowing they have the disease. In others the disease may progress notwithstanding all manner and forms of treatment. For a good many perhaps the majority, recovery and maintenance of recovery depend upon knowledge and the facilities for properly adjusting the mode of life, nutrition and environment to the amount and character of the disease, as well as the destructive conditions left in its wake.

One of its greatest dangers to the individual is that at any time it may be progressive and advance considerably without the patient being aware that a thing has happened. For this reason it is essential that the pulmonary condition be observed periodically to determine its status. The only accurate method for doing this is by means of properly taken X-ray films. While in a sanatorium these requisites are fulfilled.

The education of the patient is one of the principal accomplishments of a sanatorium residence. The knowledge of the uncertainties of the disease, the reasons why living, working and environmental adjustments must be made, as well as how much recovery and its maintenance depend upon the patient himself, all furnish the background for his care after leaving the sanatorium. In a considerable period of time after discharge, his disease is a serious potential danger.

At the beginning of sanatorium treatment the ultimate goal must be visualized. To what extent the patient will be able to return to his former work and life must be determined if possible. If he cannot fully assume the so-called "normal life," efforts should be made to fit him for work and living suitable to his condition. In other words, recreational therapy, occupational therapy, rehabilitation and the establishment of work tolerance for the patient should go hand in hand with the general treatment. The sanatorium, to complete the course of treatment, should conduct its physically able patients through all stages of rehabilitation until a maximum work tolerance of eight hours has been reached. Then the patient is fully rehabilitated. Others should be brought to their maximum work tolerance and be put on part-time work or given work in a sheltered workshop. Not all sanatoria have such a complete program. Many patients, with or without medical approval, are discharged to return to their homes and families.

The two most satisfactory guides for determining the patient's condition are the X-ray film and the patient's temperature. Of these, serial X-ray films

<sup>1</sup> Died June 8, 1946. Former Medical Director of Trudeau Sanatorium, Trudeau, New York.

us more completely the dynamic state of the 'disease. When from month to month the X-ray films show marked changes for better or worse, the disease is active, retrogressively or progressively, and rest in bed is indicated. Such is the case, too, when elevation of temperature not due to other causes is present. Other symptoms, such as loss of weight, loss of appetite, fatigue, usually mean poisoning of the body and an active state of the lesion. To determine the status of the disease, the patient should be instructed to take his temperature and pulse at least twice daily, at about 4:00 and 8:00 p.m., and to keep a record of it as well as of his toxemic symptoms, the approximate number of times he raises sputum and the approximate total amount daily. Once in six weeks, more often if deemed desirable, he should have an X-ray examination of his chest for comparison with the previous films. In old chronic disease the interval may be lengthened to several months. The weight should be watched once weekly, always at the same time of day. With such a record the physician is in a position to judge the reaction of the patient to his disease and to modify rest and other treatment as needed.

When acutely active disease is present, complete bed-rest is needed. As the activity subsides, bathroom privileges may be granted. At all times, except with markedly acute conditions, recreational periods should be permitted, at first those that are purely passively receptive such as the radio; later, light finger exercises, reading, etc., with gradual rehabilitation as the circumstances permit.

Each patient is an individual and requires individual treatment. As a general rule, after the X-ray films have revealed a practically stationary lesion for several months, and there are no toxemic symptoms, the patient may become partly ambulatory. Attention should be paid to the state of nutrition. It should be seen that proper food in ample quantity is taken and that good ventilation is present at all times.

During their stay in Trudeau Sanatorium, all patients are encouraged to plan for rehabilitation. Most patients do not need any vocational change but facilities for the arts and crafts, as well as academic courses, are offered through the Saranac Lake Study and Craft Guild and through the Trudeau Sanatorium Rehabilitation program. For many years Trudeau Sanatorium has aided its patients in this respect. There, stress has been laid on the importance of rehabilitation and the establishment of work tolerance. Physicians and nurses especially have taken advantage of the opportunities offered for rehabilitation by doing medical and laboratory work of all kinds. At the present time there is a rehabilitation director to carry on the work with the patients.

Life in a sanatorium is much less tense and demanding of energy and will-power than life at home. To have attained an arrest of the disease in the sanatorium does not mean that the arrest will continue under adverse environmental and nutritional conditions. Vigilance is needed to safeguard whatever stage of recovery has been attained.

It is true that without the tubercle bacillus we can have no pulmonary tuberculosis. It is likewise thought that the tubercle bacillus remains alive in the human body for many years after health apparently has been restored. For

this reason emphasis is laid upon the factors which contribute to the ment of the disease and its relapse or recurrence after recovery apparent place. For the patient to spend a long period of time in a favorable environment recovering from the disease, only to return to an unfavorable life, in many instances is a waste of money. Tuberculosis is essentially a chronic disease; in such a disease education in how to live with it and relapse is of extreme importance. Readjustments must be made continuously and should be made by someone familiar with all factors influencing the disease. To follow its progress, a physician who knows the picture as a whole. To be successful in the treatment of tuberculosis must go on long after discharge from the sanatorium.

What the sanatorium does or can do for a patient is briefly outlined. Postsanatorium care and complete rehabilitation are but an extension of the sanatorium activities. Vigilance should be the key note of this extended treatment, vigilance on the part of the patient and on the part of his physician.

One can give no fixed procedure for subsequent observations of the discharged sanatorium patient. The frequency of such observations of course will vary very largely on the status of the disease at the time of discharge. For a patient whose disease is arrested at discharge, an X-ray examination once every six months for a period of two years probably would be sufficient, provided the patient feels well and has no symptoms referable to the disease. To a patient discharged as apparently arrested or quiescent, I advise to have X-ray examination at least every two or three months for a period of one year and then every six months for another year; after that, if all goes well, once yearly for four years. The X-ray examination however should not be the whole story. At the time it is made there should be a consultation with the tuberculosis physician during which the patient should outline his daily routine of life, his business and home environments, so that, if it is thought advisable, adjustments to new conditions or to alter the old way may be recommended.

Shortly after Dr. Lawrason Brown took over the medical administration of the Trudeau Sanatorium, he made an effort to find out what happened to discharged patients. From such information it was thought a good deal could be learned about the postdischarge behavior of tuberculosis and at the same time the patient would be reminded of the necessity for periodic examination and consultations regarding the status of his disease. Once each year, in the anniversary month of his discharge, the patient is sent a blank to fill in. The questionnaire, in addition to a request for notice of change in address, asks about the patient's health, his work, his earning capacity, etc. The first question is "Are you as well as when you were discharged from the sanatorium?" The next, "Have you relapsed within the past year? If so, please state the date, place and cause." Information regarding current symptoms is requested as well as the result of the last sputum report and the weight. The patient is asked to give the character of his present work, the number of hours he works and his earning capacity compared with what he earned before becoming ill. Information is made as to any surgical procedures, especially collapse therapy of all kinds.

in pneumothorax the length of time treatment was continued. The dates of the most recent examination and X-ray film are requested as well as the name and address of the tuberculosis physician attending the patient. Our questionnaires meet with good success in that replies are received from about 90 per cent or more of the patients. They are returned by the patient, a member of his family, his physician or by someone interested in the patient.

Many valuable statistical studies have been made from the data thus received and much remains to be done. At the same time the patient once yearly is reminded to have a check-up of his condition. The sanatorium staff is always glad to advise the patient when requested to do so and they welcome an opportunity to coöperate with outside physicians. The patient is told that the staff will gladly examine his chest films at the request of his physician and that he may return to the sanatorium at any time for a check-up. Such a check-up affords an opportunity for the attending physician to utilize the specialized services of the sanatorium staff, which is more important if he is not specially trained in tuberculosis.

In this way the patient is made to feel that the sanatorium retains its interest in him and that he may utilize the services of the institution should he so desire. It is the essence of teamwork that the physician attending the patient be kept fully informed about the findings and recommendations of the sanatorium staff.

The treatment of tuberculosis should be carried on over many years, even if there has been an apparent restoration of health. A knowledge of tuberculosis and its many and varied behaviors is needed by him who would carry out such treatment with skill. It must be recognized that in all cases X-ray films give the most accurate estimate of what is going on in the lungs. Overcoming the disease is a matter of years, even in the earlier stages. The sanatorium lays the preliminary groundwork in education and provides satisfactory environmental and nutritional standards, but the treatment must go on after the patient has been discharged. It is highly important that the patient be made to realize this and the sanatorium should endeavor to make periodic check-up examinations of all its patients. Not only does the sanatorium staff learn many medically interesting facts, but the patient is kept aware of the necessity for constant vigilance regarding his health. Prevention of relapse is of greater importance than treatment after relapse has occurred.

#### SUMMARY

1. A periodic observation of the pulmonary condition of patients after discharge from tuberculosis hospitals is essential.
2. When the disease is active retrogressively or progressively, rest in bed is indicated.
3. Postsanatorium care and complete rehabilitation should be an extension of the sanatorium activities.
4. Each patient discharged from Trudeau Sanatorium is reminded once yearly to have a check-up of his condition and is invited to return to the Sanatorium for this.



5. *Prevention* of relapse is more to be desired than treatment *after* has occurred.

#### SUMARIO

1. La observación periódica del estado pulmonar del enfermo después de darlo de alta de un hospital para tuberculosos es indispensable.

2. Si la enfermedad se muestra activa retro- o progresivamente, el repocasma está indicado.

3. La asistencia postsanatorial y la rehabilitación absoluta deben con una prolongación de las obras del sanatorio.

4. A todo enfermo dado de alta del Sanatorio Trudeau se le recuerda un año que haga comprobar su estado y se le invita a regresar al Sanatorio a hacerlo.

5. Hay que buscar la *prevención* de las recaídas más bien que el *tratamiento* después que ocurren.

# PATHOGENESIS OF PLEURISY WITH EFFUSION<sup>1</sup>

A Clinical, Epidemiological and Follow-up Study of 190 Cases

BRIAN C. THOMPSON<sup>2</sup>

During the last twenty years, with the growth and perfection of chest radiology, there has come to be general acceptance of the view that all cases of pleurisy with effusion, in which a definite alternative etiology cannot be established, should be regarded as tuberculous and referred to the responsible Tuberculosis Authority for routine follow-up. The Ealing Chest Clinic serves an urban, industrial population, numbering 212,000, situated in the western region of Greater London, in this capacity. During the years 1937 to 1944 inclusive, 233 patients came under the care of this Clinic suffering from pleural effusion, presumed to be of tuberculous origin; that is, apart from cases of effusion occurring during the course of artificial pneumothorax treatment and those arising in patients already under observation with pulmonary tuberculosis. Of these 233 patients, there was X-ray evidence of pulmonary tuberculosis of reinfection type (phthisis) already present at the time of the initial pleurisy in 43 cases. These, it was thought necessary to exclude for the purpose of our study, which therefore is concerned with the remaining 190 patients, in whom there was, at the time of onset, either no evidence of parenchymal disease or in whom any coexistent intrathoracic lesions were indicative of a primary type of tuberculous infection only.

## MATERIAL

It is certain that not every case of pleurisy with effusion occurring in the district comes to the notice of the Clinic, but the increase in annual incidence, shown in table 1, suggests that cognizance is improving.

Vital statistics in this country include under the heading "Pulmonary Tuberculosis" all tuberculous conditions predominantly intrathoracic, including tuberculous pleurisy, without discrimination. It is therefore relevant to compare the incidence of pleural effusion with that of "pulmonary tuberculosis" in general. Table 1 shows the annual incidence of both in this district. The abrupt rise in total notifications in 1941 has been observed in the country at large (Stocks, 1944) as a phenomenon of war-time conditions. That it is apparently outstripped by the relative incidence of pleurisy with effusion may be due to more complete cognizance or may indicate a genuine epidemiological trend. The mounting figures of cases discharged from the Armed Forces favor the latter view.

In table 2 is shown the distribution by age and sex. The bulk of cases (60 per cent) occurred between the ages of 15 and 24 years. While the sex difference in the totals is not statistically significant, it is remarkable that the excess of males fell almost entirely into the 15 to 19 year group (22 cases).

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<sup>2</sup> Present address: University of Otago Medical School, Dunedin, New Zealand.

The combined age-distribution is compared with that of all other forms of pulmonary tuberculosis (2,540 cases) in the district over the same period in chart 1.

The dissimilarity of the two curves suggests at once that simple pleurisy with effusion has a pathological basis different from that of pulmonary tuberculosis in general.

*History of contact:* Contact with proved sputum-positive tuberculosis in the usual routine household investigations, was established in only 31 or 16.5 per cent of the total. This is significantly less than the figure obtained by Lloyd and Macpherson (1937) of 40 per cent in cases of phthisis in

TABLE 1  
*Annual incidence and source of cases*

	1937	1938	1939	1940	1941	1942	1943	1944
Voluntary hospitals.....	2	7	2	5	4	4	3	7
Municipal hospitals.....	4	5	11	9	14	16	11	4
General medical practitioners.....	2	3	2	5	3	4	5	13
Routine contact examination.....		1			1	3	2	1
Army, Navy, R. A. F. etc.....				3	6	7	8	13
Total.....	8	16	15	22	28	34	29	38
New cases of pulmonary tuberculosis (all forms).....	208	289	290	297	362	408	415	381
Pleural effusion, percentage.....	2.8	5.5	5.1	7.3	7.7	8.4	6.7	10.2

TABLE 2  
*Distribution by age and sex of patients with pleurisy with effusion*

YEARS OF AGE.....	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64
Male.....	1	7	6	44	23	12	5	5	1	1	1	—	1
Female.....	1	5	7	21	25	10	3	2	3	1	3	—	2
Total.....	2	12	13	65	48	22	8	7	4	2	4	—	3

adults and by Tattersall (quoted by Lloyd) of 36 per cent in a general tuberculosis population, and by Thompson (1942) of 36 per cent in sputum-positive cases.

Sometimes a contact-history illuminated not only the case in question but our general pathogenetic concepts.

*Case 168:* A man, aged 63, with an acute pleural effusion from which tubercle bacilli were isolated. No evidence was found of other tuberculosis then or subsequently. Six months later, he reported that one of a group of soldiers billeted in his home, who had a chronic productive cough, had been admitted to hospital with phthisis.

In addition to these 31 cases, there were 5 hospital nurses who might be regarded as specially exposed to infection. The 37 Services patients fall

haps into an intermediate category, as young adults coming more or less suddenly into crowded conditions and possibly into close association with occult consumptives. All but 2 were males and aged 15 to 24 years.

*Case 97:* A man, aged 22, who joined the Royal Navy in August, 1941, as a sick-bay attendant. Chest X-ray film normal on entry. In January, 1942, he was put to work on a tuberculosis ward and the following May he developed an acute pleurisy with effusion.

*Clinical features:* The presence of fluid was verified in every case by X-ray examination but a diagnostic tap was done in 125 cases only. In some of these no laboratory report was available, or it stated merely that the fluid was "sterile"

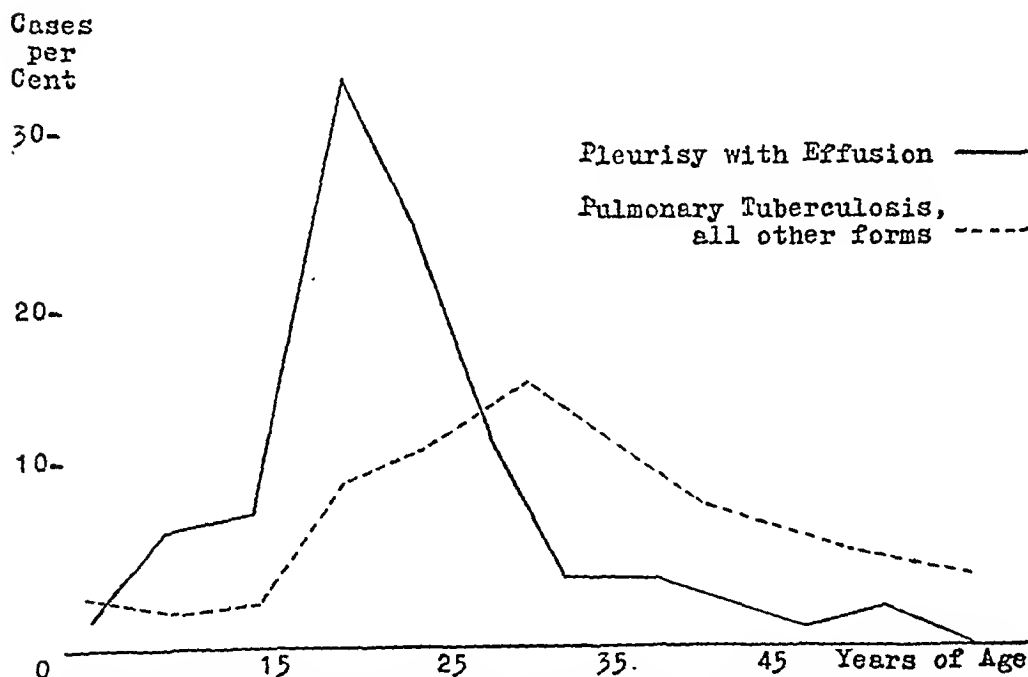


CHART 1. Ealing Chest Clinic, 1937-1944. Age distribution of 190 patients with pleurisy with effusion compared with that of 2,540 cases of pulmonary tuberculosis.

or "no tubercle bacilli found." With no standard method of examination, the number of cases in which tubercle bacilli were isolated was therefore a minimal figure. Laboratory data are presented in table 3.

*Tuberculin tests:* A positive tuberculin skin reaction was obtained in the 31 cases so tested.

*Side of the effusion:* In 111 cases the initial effusion was on the right side and in 79 on the left, a difference that is statistically significant.

In 3 of the initially right-sided cases, an effusion followed on the opposite side, after intervals of two, three and eighteen months, respectively. In 6 of the left-sided cases, contralateral effusion followed at intervals of one and a half, three, four, five, six and forty-eight months, respectively.

Bilaterality has often been regarded as an indication of hematogenous semination. Fernandez (1944) found miliary tuberculosis in the lungs of a series of 6 cases, 5 of which ended fatally. None of the 9 cases in the series presented this feature. Two of them had X-ray evidence of an primary complex at the time of the first pleurisy. One had an associated pericardial effusion and multiple osseous lesions, from which tubercle bacilli were isolated. One patient developed a tuberculous epididymitis six months later and 2 subsequently developed pulmonary parenchymal infiltrates.

*Associated intrathoracic lesions:* At or near the time of the initial pleurisy 39 of the 190 cases accepted for this study showed X-ray evidence of intrathoracic tuberculosis of other than reinfection type (table 4).

TABLE 3  
*Laboratory data on pleural fluid*

1. Tubercle bacilli isolated	.....
2. Lymphocytes predominant	.....
3. Polymorphs predominant	.....
4. Clear fluid, "sterile" or "no report"	.....
5. Chest not explored	.....
Total	.....

TABLE 4  
*Associated intrathoracic tuberculosis*

	HOMOLATERAL		CONTRALATERAL	
	Right	Left	Right	Left
Primary complex	8	2	1	2
Parenchymal focus only	11	5	1	1
Hilar adenopathy only	6	1	1	—
Total lesions	25	8	3	3

The tendency was for effusion to form on the same side as the pulmonary glandular lesion. The latter occurred much more commonly on the right side, a predilection agreed by all observers from Ghon onwards as common to the tuberculous primary complex (Kayne, 1939). In a number of cases equal effusions formed on both sides, however, the effusion was contralateral to the parenchymal glandular lesion.

The lesions described were radiologically of the type usually accepted as primary tuberculosis. In a few cases they were under observation for several weeks before the effusion formed, and it seems likely that this is the usual sequence of events. In the 18 cases where no glandular component could be demonstrated, the parenchymal lesion was in no way suggestive of reinfection pulmonary tuberculosis (phthisis), being rarely apical and often in the mid-

lower zones, nonpersistent and rarely cavitated, and leaving little or no residual fibrosis or calcification. There was one case where the right middle lobe was collapsed by pressure of caseous lymph nodes, verified by bronchoscopy, but no other instance of "epituberculosis" occurred. Obscuring of the lung fields by massive effusion or mediastinal shift notoriously impedes diagnosis, and clearing of the fluid may be accompanied by parallel clearing of parenchymal or glandular lesions, so that the above figures may be taken as minimal.

Tubercle bacilli were demonstrated in the sputum of 6 patients and in the gastric contents of 2 others. In 2 of the 8 neither parenchymal nor glandular disease could be seen; in one case there was an evanescent infiltration in the right lower lobe, in one a collapsed middle lobe (already described), in one an active primary complex and in 3 there was definite cavitation in the lung substance. In 2 other cases, intrapulmonary cavities were seen without tubercle bacilli being demonstrated.

TABLE 5  
*Development of calcification*  
1. Site of Calcification

	AT SITE OF PREVIOUS LESION	NO PREVIOUS LESION	TOTAL
Lymph node + parenchymal nodule.....	1	2	3
Lymph node only.....	1	5	6
Parenchymal nodule only.....	8	5	13
Total.....	10	12	22

2. Interval in Years

YEARS.....	-1	-2	-3	-4	-5	TOTAL
Number of cases.....	7	8	2	4	1	22

In all 5 cavitory cases, the vomica was solitary, between 2 and 4 cm. in diameter, situated in the lower and outer part of the lung field, and did not persist for more than two or three weeks. In these respects these cases were so different from the familiar cavitation of phthisis that identification with a primary lesion seems justified.

*Associated extrathoracic lesions:* In 3 cases there was associated erythema nodosum. In 2 cases there was evidence of abdominal tuberculosis concurrent with or slightly preceding the pleurisy and one further patient gave a history of *tuberculosis mesenterica* five years previously.

In one case there was an ischio-rectal abscess. There was also the case of bilateral effusion with multiple osseous lesions already described.

*Calcification:* At the time, or during the clearing of the initial effusion, calcified foci could be distinguished in only 2 cases, once as a nodule in the lung field and once in a hilar lymph node. Calcification developed subsequently in 22 cases, generally rather late in the period of observation.

As may be seen in table 5, in more than half these cases calcification was seen where no caseous lesion had previously been seen. This phenomenon was first noted by Brailey (1937) in her prolonged studies of primary infection in children and was considered by her as presumptive evidence of preceding tuberculous infection in lung parenchyma or regional lymph nodes, or both, not detected by other radiological means.

The incidence of calcification in the present series is a minimal figure for several reasons. First, no special technique, such as overpenetration or rapid exposure, was employed as routine, and a severe interpretive standard was regarded as obligatory to exclude equivocal vascular opacities. Second, had observations been longer, further instances of calcification, on the rates already found, would almost certainly have occurred.

*Treatment:* All but very few patients were treated by bed-rest in hospital and then went subsequently to sanatorium or convalescent home. Tabulation of length of stay has proved unprofitable and is here omitted. The quality of care, effusion and the use of therapeutic aspiration have similarly not been found to have any bearing on the after history.

#### THE FOLLOW-UP OBSERVATIONS

The actual process of follow-up was in itself interesting and occasionally dramatic. The great majority of patients, retained on the Clinic register for at least five years following notification, according to Ministry of Health regulations, had been regularly examined and X-rayed from the start. Tracing patients who had lapsed or who had persistently refused cooperation was made an increasingly difficult by war-time conditions. Bomb damage and evacuation of patients, abnormal removals. Homes were often vacant all day owing to all the workers being out at work. Letters might be unanswered or returned through the "wrong letter" office. Sometimes a visiting nurse was able to locate an errant patient and lure him to the Clinic, but more than once a house-to-house enquiry after working hours was necessary to get results. Single-observation technique, as in previous investigations (Thompson, 1942), is best suited to this type of work, where memory is invaluable. One girl, lost sight of since she had turned up with a reinfection lesion from a mass radiographic survey, because her name in a list of reports struck a mental chord. Another was traced after a lapse of four years, to domestic service with a doctor, who on persuasion was able to insist on her consenting to an X-ray examination, and this revealed moderately extensive phthisis. These were the only cases in which it was possible to time the onset of secondary disease. The only patient permanently lost sight of was an ex-R. A. F. pilot who unkindly emigrated to Canada twelve and a half years after his initial effusion. All other patients had the maximum possible period of observation, though there were a few cases, mostly from the earlier years, where continued X-ray studies were not available, though the patients were known to continue alive and well—removed from the district for serving in the Forces, for example. These cases of deficient radiological follow-up are detailed in table 6.

It will be seen from what follows that these radiological deficiencies were numerically too small, especially in the more important early years, to affect seriously the validity of the results.

In table 7 is shown the total subsequent morbidity and mortality from tuber-

TABLE 6  
*Radiological deficiencies*

	YEAR AFTER WHICH X-RAY STUDY CEASED				TOTAL
	1st	2nd	3rd	4th	
1937	3	—	—	—	3
1938	1	—	—	4	5
1939	2	1	—	—	3
1940	1	1	—	2	4
1941	—	1	—	—	1
1942	1	2	—	—	3
Total.....	8	5	—	6	19

TABLE 7  
*Subsequent tuberculous morbidity and mortality*

YEAR	TOTAL PATIENTS	NUMBER DEVELOPING TUBERCULOSIS IN EACH YEAR OF OBSERVATION							
		1st	2nd	3rd	4th	5th	6th	7th	8th
1937	8	—	—	1	—	—	—	—	—
1938	16	2	1	—	2	—	—	—	—
1939	15	—	2	—	—	—	—	—	—
1940	22	2	4	1	1	2*	—	—	—
1941	28	1	2	—	—	—	—	—	—
1942	34	5	1	—	—	—	—	—	—
1943	28	7	1	—	—	—	—	—	—
1944	39	5	—	—	—	—	—	—	—
Total..	190	22	11	2	3	2	—	—	—
Pulmonary.....		19	8	2	3	2	—	—	—
Extrapulmonary ..		3	3	—	—	—	—	—	—
Deaths.....			3	1	1	1	—	—	—

\* Two patients with date of onset undetermined.

culosis occurring in each year subsequent to the initial pleurisy. It will be noted that no new tuberculous lesion developed later than five years.

Dealing first with morbidity alone, it is now possible to construct a "survival" table, enumerating those patients from each year of diagnosis who remained free from secondary tuberculosis in each successive year that they continued under observation.



could not longer be followed (for example, the 34 patients from 1944 still from tuberculosis at the end of 1945, when the investigation closed), we can give the number of patients remaining at risk in each succeeding year. The observed number that actually developed lesions during each year, obtained

TABLE 8  
*Annual tuberculosis morbidity*

	PATIENTS REMAINING UNAFFECTED ON EACH ANNIVERSARY								
	0	1	2	3	4	5	6	7	8
1937	8	8	8	7	7	7	7	7	7
1938	16	14	13	13	11	11	11	11	
1939	15	15	13	13	13	13	13		
1940	22	20	16	15	14	14†			
1941	28	27	25*	24	24				
1942	34	29	28	28					
1943	28	21	20						
1944	39	34							
Total.....	190	168	123	100	69	45	31	18	7

\* One patient lost sight of in following year.

† Subtract 2 patients developing tuberculosis during preceding five years.

TABLE 9  
*Calculation of annual morbidity rates*

YEARS OF OBSERVATION (x)	NUMBER OF PATIENTS OBSERVED EACH YEAR (n)	NUMBER DEVELOPING TUBERCULOSIS EACH YEAR (q)	PROBABILITY OF DEVELOPING TUBERCULOSIS (q/n)
1st	190	22	.12
2nd	134	11	.08
3rd	103	2	.02
4th	72	3	.04
5th	45	0*	.00*

\* To this must be added 2 cases developing some time during the preceding five years by  $2/190 = .01$ ).

From table 7, divided by the number at risk, gives us the annual morbidity rates shown in the final column of table 9.

A life-table may now be constructed on the basis of 1,000 patients, for convenience of calculation, using the annual morbidity rates derived from the foregoing calculations (table 10).

Thus at the end of five years only 754 of our original 1,000 patients with pleural effusion have failed to develop tuberculosis. In other words, approximately one-quarter of the total have developed lesions; nearly one-half of these

became detected within twelve months of the onset of the initial pleurisy and more than half the remainder within the next twelve months.

*Details of subsequent tuberculosis:* For the age distribution of patients developing tuberculosis the reader is referred to a previous publication (Thompson, 1946) where this was shown to be approximately the same as for the whole 190 patients (table 11). The same applies to those cases that ended fatally. That is to say, age *per se* appears to have no prognostic significance.

TABLE 10  
*Tuberculosis morbidity in life-table form*

YEAR AFTER DIAGNOSIS (x)	PROBABILITY OF DEVELOPING TUBERCULOSIS IN THAT YEAR (dx)	NUMBER REMAINING UNAFFECTED ON EACH ANNIVERSARY OUT OF 1,000 PATIENTS (cx)	NUMBER DEVELOPING TUBER- CULOSIS EACH YEAR (dx)
0	.12	1000	120
1	.08	880	70
2	.02	810	16
3	.04	794	32
4	.01*	762	8
5	.00	754	—

\* See footnote to table 9.

TABLE 11  
*Incidence of subsequent tuberculosis*

SIDE OF EFFUSION		SUBSEQUENT TUBERCULOSIS					TOTAL SUB- SEQUENT TUBERCU- LOSIS
		Pulmonary				Extra- pulmonary	
		Right	Left	Bilateral	Total		
Right.....	108	8	8	4	20	2	22
Left.....	73	4	7	1	12	3	15
Right-left.....	3	—	—	—	—	—	—
Left-right.....	6	1	1	—	2	1	3
Total.....	190	13	16	5	34	6	40

Of the 34 patients developing pulmonary tuberculosis, 24 were females. All the 6 that developed extrapulmonary tuberculosis were males.

It is clear from table 11 that subsequent lesions were influenced neither in frequency nor in localization by the side of the preceding pleurisy.

*Pulmonary lesions:* The commonest pulmonary lesion at its earliest detectable stage was one characterized radiologically by fine stippling in the extreme apex, tending to spread downward on the same side and to be reproduced in the opposite apex. In 5 cases this type of lesion was symmetrically bilateral at its inception (table 12).

The other type of pulmonary lesion was that which appeared initially in the

upper half of the lung field below the clavicle. This was radiologically divisible into two classes: (1) diffuse, finely stippled or strand-like; (2) massive, caseous-pneumonic or smaller solitary foci (Assman type).

Both types of pulmonary tuberculosis were usually without symptoms when first detected.

*Extrapulmonary lesions:* There was one case each of tuberculosis involving the chest wall, epididymis, vertebrae, shoulder-joint, peritoneum and meninges. The last 3 cases ended fatally.

*Prognosis:* Local progression of pulmonary lesions, of whatever type, tended to occur, as in similar lesions that we encounter without a pleuritic history. In a few cases, especially those with solitary or Assman foci, resolution took place rapidly, within weeks or months. In 2 cases hematogenous dissemination occurred to epididymis and spine, respectively.

The course of the disease was no doubt to some extent influenced by its discovery at the earliest possible stage and by its immediate treatment. For this

TABLE 12  
*Subsequent pulmonary tuberculosis—Classification of lesions*

	APICAL	SUBAPICAL		TOTAL
		Diffuse or nodular	Massive or solitary foci	
Right side.....	7	4	2	13
Left side.....	6	2	8	16
Bilateral.....	5	—	—	5
Total.....	18	6	10	34
Tubercle bacilli in sputum .....	5	5		10
Dead.....	2	1		3

reason, and because observation has been relatively short, we can draw no far-reaching conclusions about its ultimate outlook. It is very likely that many of the lesions which have become apparently arrested will in later years break down in the catastrophic manner of this insidious and unpredictable disease.

*Mortality:* The 6 deaths that have so far occurred may be statistically treated by the same technique as that adopted for tuberculosis morbidity (tables 7 to 10). This method, the details of which need not be repeated, gives us a case-fatality rate for the whole 190 patients of 3.5 per cent over a five year period from the date of the initial pleurisy.

#### DISCUSSION

The concept has been gaining ground in recent years of simple pleurisy with effusion as a direct outcome of, or even as a stage in the development of, a primary tuberculous infection of the respiratory tract. Erwin (1944) has given *a priori* reasons why an intrathoracic primary complex may be expected on

occasion to produce direct infection of a highly allergic pleura, tubercle bacilli penetrating either from a subpleural parenchymal focus or from a caseous tracheobronchial lymph node. Such an explanation would fit the facts observed in this series better than the alternative assumption of a postprimary dissemination by the blood-stream. Only rarely was there gross evidence of the dispersed foci that would be expected in such an event. Miliary pulmonary disease was never encountered. Bilateral effusions were few and never simultaneous.

In contradiction to the symmetry demanded by a hematogenous theory, unilaterality was a pronounced feature. Right-sided effusions predominated, as right-sided primary lesions are known to predominate. Where primary lesions were in fact demonstrable, these were most commonly on the right side and were most commonly associated with right-sided effusions. Those apparently anomalous cases, in which effusion occurred on the side opposite to a manifest primary lesion, may very well be explained as a direct extension of infection by way of a chain of tuberculous lymph nodes across the mediastinum; in such chains observed at autopsy the most grossly affected of the nodes may be one relatively remote from the primary focus.

If this explanation is correct, it is curious that pleurisy with effusion is so uncommon in childhood, when primary infection with tuberculosis so frequently occurs and when the primary intrathoracic complex is most often observed. The peculiar age-incidence of pleurisy with effusion, with its predilection for late adolescence and young adult life, is found regularly in all large series of cases. Conversely, in a personal series of 1,050 children in contact with known tuberculosis, 693 of whom were tuberculin-positive and 52 others of whom became converted from negative to positive, I found 66 cases of active primary tuberculosis within the thorax but only 2 of pleural effusion. It would appear therefore that age introduces an important factor in the pathogenesis of this condition. Vilén (1941) has shown that the age-distribution of pleurisy with effusion in Gothenberg has remained unchanged after forty years, although during the same period the age at which first infection with tubercle bacilli occurs has advanced steadily.

Primary tuberculous infection in adults, as evidenced by a change in tuberculin sensitivity from negative to positive, may be followed after a short interval by an attack of pleurisy, without other manifest intrathoracic tuberculosis (Israel and Long, 1941). Arborelius (1930) found that one-third of his adult patients with demonstrable primary lesions developed pleurisy with effusion within six months. Brooks (quoted by Robson, 1944) records a similar occurrence in 6 out of 63 Naval personnel in whom a primary type of lesion was discovered by mass radiography. Matte and Saldias (1944) describe 50 school-age children with primary tuberculosis, of whom 21 developed effusions within six months. That the only considerable series in children should come from Latin America, where sexual maturity comes early, is perhaps significant. Edwards (1945), who retests his tuberculin-negative nurses at monthly intervals and so is able to time their conversion very accurately, regards six months as an average interval before pleurisy intervenes, an opinion borne out by the Prophit

Study on infection in nurses (Daniels, 1944) though the total cases observed by these workers are very few in number. The present series contains no information on Mantoux conversion. Its high incidence, however, of gross florid primary lesions within the thorax suggests that not all these had been present many months before detection; some at least were probably only a few weeks old.

Calcification in the hilar region or in the lung field was present initially in only 2 cases, a very low figure for an urban population of this age-distribution. The presence of calcified foci, presumptive evidence in England of old tuberculous infection, was therefore rare enough to suggest a group low in tuberculosis experience. On the other hand, it does not mean that these 2 patients could not have undergone a recent second primary-type infection, the previous one having become obsolete, the possibility of which has been shown by Terplan (1946) and others. The occurrence of calcification subsequent to pleural effusion (table 5) confirmed in some cases the caseous character of lesions noted previously and also increased the probable incidence of such lesions. That relatively few of the gross primary lesions underwent calcification is in accordance with the usual finding (Rich, 1944) that the primary complex in adults calcifies less frequently and less massively than in children.

The low incidence of known contact with tuberculosis, the large number of cases derived from relatively fresh entrants into the Armed Forces, and the excess of males in the 15 to 19 year group—all point in the same direction: to a young person who escapes first tuberculous infection in childhood, at home or at school, to meet it suddenly and perhaps in a single massive dose in the unaccustomed hurly-burly of industrial or barrack life.

The picture is indeed almost complete. Its foreground is filled in by subsequent developments. Pulmonary tuberculosis of reinfection type ensues in a high proportion of cases, usually quite soon. In many cases, within a few months or even a few weeks of the original pleurisy, a clear lung field becomes the seat of the first tiny deposits. Without exposure to repeated external tuberculous infection, the endogenous source of this disease is certain and one cannot but see the whole process as continuous from primary infection through pleurisy with effusion to phthisis. That the latter must often progress to a stage of self-limitation, characterized by the formation of fibrotic boundaries and excavation, before artificial therapy can become effective, though outside the scope of this paper, further endorses this view, with the additional, if uncomfortable, rider that up to that point it is possibly beyond the physician's control and, in that sense, inevitable.

The incidence of extrathoracic, as opposed to pulmonary reinfection tuberculosis, suggests that both types of disease have a hematogenous derivation; this is to some extent confirmed by the character of the commonest pulmonary lesion, a fine apical seeding, often becoming bilateral.

#### SUMMARY

A study is presented of 190 cases of simple pleurisy with effusion.

There was a high incidence of preceding or concurrent intrathoracic lesions

typical of primary tuberculosis, confirmed sometimes by the later development of calcification. Cavity formation occurred in 5 cases presenting these lesions. The lesions, glandular or parenchymal, were not always on the same side as the effusion. The incidence, both of primary-type lesions and of pleural effusion, was higher on the right side than on the left.

Pleurisy with effusion was found predominantly in the years of late adolescence and young adult life. There was an excess of males over females confined to the 15 to 19 year group.

The follow-up for the maximum periods of one to eight years was virtually complete. It revealed subsequent tuberculosis in 12 per cent of the total patients within the first year, in 8 per cent of the remainder within the second year and in a total of 25 per cent within five years. No case occurred after five years. In 15 per cent of these cases the first evidence of disease was extrapulmonary.

The death rate for the 190 patients over the five-year period was 3.5 per cent.

The age of the patient bore no demonstrable relation to the incidence of subsequent tuberculosis or to its prognosis.

#### CONCLUSIONS

Pleurisy with effusion has probably increased in frequency under war-time conditions in England, reaching an incidence equal to one-tenth of all intrathoracic tuberculosis.

In the absence of evidence of reinfection tuberculosis and of a definitely non-tuberculous etiology, it is usually a manifestation of a recent primary tuberculous infection.

It is typically a condition of young adults, in whom the reaction to such an infection is different from that of children. Pleural effusion in the latter is relatively uncommon.

The evidence suggests that postponement of first infection by the tubercle bacillus to post-adolescence is quite likely to result in pleurisy with effusion, with or without demonstrable intrathoracic primary lesions, often within some weeks of the development of tuberculin sensitivity but usually within six months.

One-quarter of all cases go on to develop systemic tuberculosis, the earliest evidence of which often becomes detectable within a few months of the onset of the pleurisy, usually within a year and almost always within two years. In 85 per cent of these cases the disease is in the first instance localized in the lung.

It would appear that these phenomena are each and all part of a continuous pathological process, which may become arrested at any stage in its progress or may, at the other extreme, advance to a fatal conclusion. The material offers only a provisional or minimal figure for this latter probability.

There is no evidence of any factor that may influence this march of events. Its apparent inevitability may lead one to speculate on the potentiality of medical treatment for its arrest or modification. This seems no reason, however, for neglecting such means as are already in general acceptance: bed-rest during the acute phase, prolonged convalescence, careful radiological supervision for

five years and appropriate handling at the earliest possible moment of such pulmonary or extrapulmonary tuberculosis as may arise.

### CONCLUSIONES

La pleuresía con derrame ha aumentado probablemente debido a las condiciones del tiempo de guerra en Inglaterra, alcanzando una incidencia equivalente a la décima parte de toda la tuberculosis intratorácica.

Cuando no hay signos de tuberculosis tipo reinfección o de una etiología claramente no tuberculosa, suele ser una manifestación de una infección tuberculosa primaria reciente.

Es típicamente un estado de los adultos jóvenes, en quienes la reacción a una infección de ese género es distinta de la de los niños, pues en éstos el derrame pleural es relativamente raro.

Los datos disponibles indican que el aplazamiento hasta la postadolescencia de la primoinfección por el bacilo tuberculoso dará probablemente por resultado pleuresía con derrame, con o sin lesiones primarias intratorácicas observables, a menudo a las pocas semanas de presentarse la sensibilidad a la tuberculina pero por lo general en término de seis meses.

La cuarta parte del total de casos avanza hasta manifestar tuberculosis orgánica, cuyos primeros signos pueden frecuentemente descubrirse a los pocos meses de la iniciación de la pleuresía, por lo general en término de un año y casi siempre de dos años. En 85 por ciento de esos casos la enfermedad se encuentra en primer lugar localizada en el pulmón.

Según parece todos esos fenómenos y cada uno de ellos forman parte de un continuo proceso patológico, que puede estacionarse en cualquier etapa de su marcha, o por el contrario, proseguir hasta un desenlace fatal. El material estudiado no ofrece más que cifras provisionarias o mínimas para la última probabilidad.

No hay datos relativos a ningún factor que pueda afectar la marcha de los acontecimientos, y su aparente inevitabilidad tal vez conduzca a especulaciones referentes a las potencialidades del tratamiento médico con respecto a estacionamiento o modificación. Sin embargo, no parece que haya motivos para descuidar los medios que ya gozan de aceptación general: reposo en cama durante la fase aguda, convalecencia prolongada, cuidadosa vigilancia radiológica durante cinco años, y atención apropiada cuanto antes a toda tuberculosis pulmonar o extrapulmonar que se presente.

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## MULTIPLE INFECTIONS IN HUMAN TUBERCULOSIS<sup>1</sup>

ALF WESTERGREN<sup>2</sup>

In a lecture on March 28, 1944, before the Swedish Medical Society, entitled *The Concept of Rheumatic and Tuberculous Pleurisy in the Light of the Antistreptolysin Reaction*, I reported on a study of 172 cases of pleurisy. I emphasized the importance of multiple infections, particularly associated with tuberculosis, and stressed at this point especially that nearly half of the cases of acute tuberculous pleurisy showed positive signs of  $\beta$ -hemolysing streptococcus infection which nowadays is regarded as the cause of "rheumatic" disease. Some 10 cases of pleurisy, most of them combined with pneumonia, in which the tuberculous etiology was uncertain or rather put off, had all shown rather low AST (antistreptolysin titer). Since then further intensive study of multiple infections has been carried on at St. Görans Hospital in Stockholm, in coöperation with the Swedish State Laboratory of Bacteriology.

The material comprises now approximately 20,000 samples from about 3,000 cases. As related in the above mentioned lecture, we were at the time looking for a corresponding serological reaction for the study of the influence of non- $\beta$ -hemolysing streptococci on the organism, and Adamson was able to report that same year good results with a precipitin reaction (*Nordisk medicin*, 1945, 27, 1671). For technical reasons the test was put aside, but we now intend to resume it with an improved technique. However, Packalen has, in addition to pure bacteriological research on a large scale, also carried on serological studies on the influence of staphylococci which are to be published and Adamson will report on the bacteriological research on autopsy material, which has yielded results that should also prove of interest.

The material of pleurisy cases followed by antistreptolysin tests (and to a certain extent also by the other aforesaid tests) amounts now to approximately 600 patients, of whom 354 can be counted as acute pleurisy (examined by antistreptolysin tests within three months from the first symptoms of pleurisy). Of these, 157 cases or 44.4 per cent, showed AST over 200 (that is, definite pathological increase). In 118 of these 157 cases there were no, or quite insignificant, lesions in the lungs, and no progressive tuberculosis as a sequel to the pleurisy was observed. The frequency of AST above 200 in this type of cases is 44.7 per cent. Considerably higher frequency (77.8 per cent) was found in cases of pleurisy without pulmonary lesions in which progressive tuberculosis was later observed, whereas in patients with acute pleurisy, in whom a previous tuberculosis of the lungs had existed, a lower frequency of pathological AST (34.7 per cent) was observed.

If these cases are studied with respect to the amount of the exudate, height and duration of temperature and sedimentation rate, it is found that 37.6 per

<sup>1</sup> Lecture given before the Swedish Medical Society, February 26, 1946.

<sup>2</sup> Chief Physician, Medical Tuberculosis Department, St. Görans Hospital, Stockholm, Sweden.

cent of the cases with a relatively small exudate have a high AST, as compared to 51.8 per cent of cases with a large exudate. In cases with low temperature the AST is above 200 in 37.8 per cent; in cases with high temperature in 52.9 per cent. When the sedimentation rate is below 50 mm., the AST is above 200 in 33.8 per cent, but the percentage is 51.9 per cent of the cases with higher sedimentation rates. Of the 71 cases which have shown a small exudate as well as low temperature and comparatively low sedimentation rate, 22, that is, 30.9 per cent, have a high AST, but of the cases with large exudate in conjunction with high temperature and high sedimentation rate (this group also comprises 71 cases), no less than 61.9 per cent have an AST over 200.

Four hundred sixty-six cases of pleurisy, observed at a later period (from three months up to two and three years), show in 34.7 per cent an AST above 200 (against 44.5 per cent in the acute cases). In the cases of the group which have no definite parenchymatous changes a high AST is found in 30.5 per cent. Cases with progressive tuberculosis have an AST above 200 in 68 per cent. Cases in which evident pulmonary lesions have been found, either before or after the pleurisy, have a high AST in 32.4 per cent.

These figures show that a high AST, as an effect of  $\beta$ -hemolysing streptococci, does not strictly parallel the intensity of the pleurisy or the prognosis, but that there is an unmistakable tendency in this direction. Thus the very acute cases of pleurisy, and the cases where tuberculous lesions appeared, manifest a greater frequency of a high AST.

The influence of hemolysing streptococci is a fairly common occurrence, not infrequently found among practically healthy persons. Even a titer of 100 is, strictly speaking, not normal. Statements in the literature concerning AST in "normals" vary within rather wide limits. English and American authors (with material of several thousands of cases) as a rule report AST values between 100 and 200 units in 2 to 20 per cent of the cases and titers above 200 in 2 to 6 per cent. The majority of Scandinavian authors seem to have found somewhat higher values, 10 to 15 per cent of their cases showing AST above 200 units. It is not clear whether this difference depends on infections with hemolytic streptococci being more common in the Northern countries or whether their material is selected with different degrees of accuracy. AST above 200 must, however, also in our work be considered as "definitely pathological" but should not necessarily be interpreted as a sign of importance.

In the now quite extensive literature on AST, values of over 200 units are recorded in approximately 90 per cent of patients with *angina tonsillaris*, scarlet fever, acute rheumatic polyarthritis and acute glomerular nephritis. In chronic polyarthritis and chronic nephritis the published data vary, but elevated AST are usually of considerably lower frequencies (10 to 50 per cent).

Lofgren's research on erythema nodosum, published in 1943, showed AST above 200 in approximately 55 per cent of the cases (his material is assembled from 152 cases and he gives the figure as 42 per cent (Acta med. Scandinav., 1946, Suppl. 174)). Much the same conditions seem to exist concerning other types of streptococci, and also staphylococci, these bacteria showing similar

signs of nosogenic influence in cases of tuberculosis as the  $\beta$ -hemolytic streptococci. Even other microorganisms, more or less pathogenic, very likely ought to be considered. (See also Westergren, *Acta dermat.-venereol.*, 1946, 26, 384.) In my material of acute tuberculous pleurisy (111 cases), presented in 1943 and 1944, a high AST was found in 41 per cent (in the present material of 344 cases in 44.4 per cent). I have now undertaken a preliminary survey on high AST in tuberculosis of the lungs (with no preceding pleurisy or erythema nodosum) and have found the frequency in 360 cases to be 35.5 per cent, a figure of the same magnitude as that in cases of subacute, chronic or recently healed pleurisy. This rather heterogeneous group showed, as above stated, a high AST in 34.7 per cent of the cases. Another group of 172 cases of tuberculosis of the lungs, in which pleurisy is generally further back in the anamnesis, has shown a somewhat lower frequency of AST above 200, namely 28.5 per cent. It can be stated here that Adamson found precipitin titers, indicating an effect of non- $\beta$ -hemolysing streptococci, in 44 per cent of miscellaneous tuberculous material comprising 434 cases, but only in 7 per cent in 63 practically healthy persons.

A preliminary checking of 462 cases with a variety of medical diseases shows AST above 200 in 83.3 per cent in acute polyarthritis and the other diseases, mentioned above, which are assumed to be caused by streptococci (40 cases). (Seventeen cases of pulmonary tuberculosis are not included in the material mentioned above. Of those with similar complications 82.3 per cent had a high AST.) The other medical cases (422) showed a correspondingly high AST in 17.0 per cent; 129 among these consist of chronic joint, kidney and pulmonary diseases (not tuberculous) and of skin diseases. This group has high AST in 24.8 per cent of the cases, and the frequency figure for the remainder (293 cases) of medical material (acute and chronic diseases) comes to 13.7 per cent. (Hepatic diseases have been entirely excluded in this connection.)

Even if the influence of hemolytic streptococci, generally speaking, may be somewhat more common than is to be gathered from the heretofore available literature, pathologically high AST is observed in a strikingly large percentage of cases of tuberculosis. Among many, high AST (as well as low) makes a relatively constant appearance, but increases and decreases in connection with the tuberculous processes can often be noted. Much the same conditions seem to exist in regard to other types of streptococci and staphylococci. These bacteria show similar signs of a nosogenic influence in tuberculosis. Other microorganisms of questionable pathogenicity may also have to be considered.

#### SUMMARY

"Mixed infection" and "secondary infection" in tuberculosis have been discussed previously as a complication of manifest tuberculous disease. Experience with erythema nodosum and pleurisy has shown remarkably high frequencies of increased AST. This seems to indicate an occurrence of a far more general interest. It must thus be a question of an important synergism of multiple infections, which is especially noticeable at an early stage in the development of tuberculous lesions.

## SUMARIO

Ya se han discutido la "infección mixta" y la "infección secundaria" en la tuberculosis como complicaciones de la enfermedad tuberculosa manifiesta. Las observaciones realizadas en el eritema nudoso y la pleuresía han revelado una frecuencia notable por lo alta de la titulación de antiestreptolisina, lo cual parece reflejar un hecho de importancia mucho más general. Debe tratarse, pues, de un importante sinergismo de las infecciones múltiples, que se observa particularmente en una etapa incipiente en el desarrollo de las lesiones tuberculosas.

# THORACOPLASTY FOR PULMONARY TUBERCULOSIS<sup>1</sup>

## Observations on 32 Patients in the Older Age Group

PAUL E. ZUELKE, W. E. ADAMS AND ROBERT G. BLOCH

Thoracoplasty is well entrenched in the surgical treatment of pulmonary tuberculosis and the type of patient suitable for the operation, except for age, is pretty universally agreed upon. In the early days of thoracoplasty, patients 40 years of age seemed to be the upper limit at which it was considered advisable. This arbitrary age limit has gradually been revised upwards but there is still a great deal of hesitancy in using the operation in older patients, particularly in those over 50.

Decker (1), in reporting 17 cases of thoracoplasty in older patients, concluded that thoracoplasty should be used with greater precaution and hesitancy in the older age groups and that other collapse procedures should be tried first. Davies (2) said that, although no age limits can be given, it is generally inadvisable to perform thoracoplasty in patients over 45 years of age because of the likelihood of cardio-respiratory changes and the diminished ability of the remaining lung to compensate for the loss of aerating surface.

More recently results have been published which are at variance with these earlier works and they generally give a better outlook for the older patient. Overholt (3), reporting in 1940, on 162 patients between 40 and 65, showed:

	<i>Per cent</i>
Sputum conversion.....	87
Benefited.....	84
Operative and early fatality.....	6.8
Late fatality due to tuberculosis.....	4.0

He concluded that "patients who have reached the latter decades of life should not be denied the benefits of permanent collapse therapy on the grounds of age alone."

Shapiro and Munz (4), reporting on 47 cases between 40 and 60, had 52 per cent conversions, 30 per cent non-conversions and 18 per cent fatality. They concluded that "patients in this group can stand the operation of thoracoplasty as well as younger individuals providing they meet the requirements of an elective operation."

Rudolph (5), reporting on 123 patients, 82 of whom were between 40 and 57, concluded that "with proper selection, men from 40 to 60 years of age stand the rigors of thoracoplasty almost as well as those from 20 to 40. However, the older patients do not convert as readily or as quickly."

This particular study was undertaken because of the rather wide-spread belief that thoracoplasty in older patients gives poor results and because in a number of tuberculosis Sanatoria a thoracoplasty is not advised for patients

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over 50 years of age. This refusal often dooms these patients to years of sanatorium care away from their families who may need their services as wage earners.

The statistical importance of this group has been shown by various studies. Overholt's report (3) was based on results in six sanatoria in New England having a total capacity of 1,213 beds. Thirty-two per cent of these patients were over 40 years of age and 18 per cent were over 50. In a recent study made on the Negro population at the Provident Hospital in Chicago, 25,000 patients were fluoroscoped and X-ray films were made if indicated. This was done as a routine on all patients seen at the hospital plus a large number of people with no illness or complaints whatsoever. This study showed a gradually increasing prevalence of clinically important tuberculosis in the older age groups as follows:

	<i>Per cen</i>
20-29.....	2.9
30-39.....	2.6
40-49.....	2.7
50-59.....	3.3
60-69.....	3.1
70+.....	6.2

The disease in many patients in these age groups has come to an impasse because of the mechanical effects of fibrosis and pleural adhesions which prevent adequate collapse of their cavities by any means other than thoracoplasty. Since they have lived as long as they have, they probably have a considerable resistance to their disease and thus are often better operative risks than younger patients with the more exudative forms of the disease. Their cavities, however, with their constant discharge of tubercle bacilli, are a serious threat to their own lives as well as a menace to society. Therefore they must be isolated.

Positive sputum seems to be the primary consideration in these people. They are usually patients on whom various forms of collapse therapy have been tried to no avail and on whom no amount of bed-rest will effect a cure. Furthermore, they are a danger to others because in many cases they have children or grandchildren with whom they come in repeated contact and from whom they should be separated.<sup>2</sup> Consequently, they take up beds in our already overcrowded sanatoria which might better be put to use in arresting a case of early tuberculosis which could be cured by bed-rest alone. Further, these older patients usually make a poor psychological adjustment to prolonged sanatorial care and many would choose the small added discomfort of a thoracoplasty and a chance at permanent cure rather than to remain, perhaps for the rest of their shortened lives, in a sanatorium.

In evaluating the results of thoracoplasty one must keep in mind what would happen to these patients if thoracoplasty had not been done. Freedlander (6) reported results in 143 patients, 85 of whom accepted thoracoplasty and 58 refused. In his operated group there were 57 per cent cavity closures and, in

<sup>2</sup> One of these patients in our series infected his 35 year old daughter before he could be isolated and treated. She developed cavitation but later cleared up on bed-rest.

TABLE 1  
*Duration of disease in different age groups*

DURATION OF DISEASE IN YEARS	40-49 YEARS 20 CASES	50-59 YEARS 8 CASES	60-65 YEARS 4 CASES	AVERAGE
0-1	0	2	1	9 years
1-5	7	2	2	
5-10	4	1	0	
10+	0	3	1	

TABLE 2  
*Treatment prior to thoracoplasty*

PROCEDURE	40-49 YEARS 20 CASES	50-59 YEARS 8 CASES	60-65 YEARS 4 CASES
Phrenicus exeresis.....	5	1	0
Pneumothorax.....	13	2	0
Bed-rest	12	2	2
(Average 1.5 yr.) { Less than 1 year.....	4	2	2
{ 1-5 years.....	4	4	0
{ 5 years+.....			

TABLE 3  
*Condition of lungs before thoracoplasty*

	40-49 YEARS 20 CASES	50-59 YEARS 8 CASES	60-65 YEARS 4 CASES
Cavitation.....	19	8	3
Unilateral involvement.....	14	4	2
Bilateral involvement.....	6	4	2
Apical involvement.....	19	8	3
Other lobes involved.....	1	1	1

TABLE 4  
*Condition of sputum before thoracoplasty*

	40-49 YEARS 20 CASES	50-59 YEARS 8 CASES	60-65 YEARS 4 CASES	AVERAGE
Hemoptysis.....	13	6	0	45 cc.
Amount per day { 0-10 cc.....	3	3	0	
{ 10-50 cc.....	11	3	1	
{ 50 cc.....	6	2	3	
Positive sputum.....	20	8	4	

those refusing the operation, there were only 10 per cent closures. Also there were almost twice as many deaths in the unoperated patients.

In the Provident Hospital series cited above there was a one- to three-year follow-up on all of the clinically important cases. In the patients originally classified as far advanced, 31 per cent had remained stationary or had improved, whereas 69 per cent had become worse or died. Only 13 per cent of this group received any treatment and none of them received a thoracoplasty.

The outlook is dark indeed for the tuberculous patient who is not adequately treated. When other means have failed, a thoracoplasty may offer the only chance many of these patients have for living a satisfactory life.

These patients are being reported because they appear to substantiate the conclusions reached by Overholt, and Shapiro and Munz, and Rudolph, and because several of the patients upon whom excellent results were obtained had been refused thoracoplasty elsewhere because of their advanced age.

The series consists of 32 consecutive patients between the ages of 40 and 65 operated on by one of us (W. E. A.) between 1933 and 1945. These patients were all classified as far advanced, 30 having cavitation visible on X-ray films and all 32 having a positive sputum.

Age *per se* was never a factor in determining the operability of a patient. Instead, each individual was judged on the basis of his general condition as to whether he met the requirements of an elective operation. The pulmonary reserve was estimated by the X-ray appearance of the lungs, by the bilaterality of the disease and by the extent of fibrosis and emphysema. Vital capacities were determined on most of the patients. These served mainly to show that patients with vital capacities below 1,000 cc. are extremely poor risks. The 2 operative deaths in this series occurred in women with vital capacities of 820 and 1,050 cc., respectively. Bronchspirometry, to determine the efficiency of each lung separately, would probably add a great deal in evaluating the pulmonary reserve. However, it was not available in these cases.

The cardiac status was determined by the size of the heart, by X-ray examination, history of cardiac disturbances, and electrocardiograms where they seemed indicated. Kidney function was tested by routine laboratory tests supplemented by urea clearances when necessary.

The duration of the disease, as shown in table 1, was difficult to determine. Some patients gave histories of chronic cough for years but did not come in for treatment until they had had a hemoptysis. Others had known of their tuberculosis for many years, some as long as twenty-three years, a good share of which time had been spent in sanatoria. No difference was seen in the results between those having the disease a long time and those having had it a short time.

The majority of patients had had some form of treatment prior to thoracoplasty, as shown in table 2. Most of this had proved ineffective or only of temporary benefit. Many had been hospitalized for varying periods of time.

The condition of the lungs before thoracoplasty, as determined by X-ray films, is presented in table 3. One patient had numerous cavities in both apices and another had a cavity in the lower lobe as well as one in the apex which pre-neco-exeresis had failed to close.



The status of the sputum before surgery is given in table 4. All patients had a positive sputum, as high as Gaffky X in several instances. A history of hemoptysis was given by 19 patients, and was the presenting complaint in several instances. The volume of sputum varied tremendously. Some patients raised 200 to 300 cc. every day while others had very little.

#### OPERATION

The operations were all done under ethylene + oxygen anesthesia. Pre-operative medication consisted of 0.18 g. calcium nembutal and 0.01 g. morphine sulphate. The patients were all awake before leaving the operating room. The cough reflex was thus depressed for as short a time as possible. The number of stages done on each patient is shown in table 5. Long segments of three ribs were usually removed at each posterior stage. One-half of the patients received anterolateral supplementary operations in addition to the paravertebral stages.

TABLE 5  
*Number of stages*

	40-49 YEARS 20 CASES	50-59 YEARS 8 CASES	60-65 YEARS 4 CASES
Paravertebral { 1 stage.....	3	3	0
{ 2 stages.....	13	5	2
{ 3 stages.....	4	0	2
Anterolateral.....	12	2	2
Revision.....	0	0	1
Total—81 (Average: 2.5).....	53	15	13

In only 2 cases was it necessary to remove more than seven ribs. If the patient underwent the operation without difficulty, the next stage usually followed in two weeks in order to obtain the maximum amount of collapse before there was regeneration of bone in the beds of ribs previously resected. Only one revision thoracoplasty was necessary. This was on a man whose sputum had remained positive despite four previous stages. Blood transfusions were used freely; 60 transfusions were given for the 81 stages.

The complications, as shown in table 6, were surprisingly few. The patients as a whole stood the operation very well. Five patients had febrile reactions following the operation which usually consisted of daily spiking temperatures of 39° to 40°C. for several days. This was interpreted as indicating a tuberculous spread or reactivation of preëxisting lesions. These all cleared up in two to three weeks.

The vital capacity of 2 patients following thoracoplasty was much reduced and they complained of dyspnea on exertion. However, they have been able to return to part-time work. There were no deep infections in this series and only 2 patients had superficial wound infection which required postponement

TABLE 6  
*Complications*

	40-49 YEARS 20 CASES	50-59 YEARS 8 CASES	60-65 YEARS 4 CASES
Febrile reaction { Probably indicating spread or reactivation..	4	1	0
Respiratory insufficiency.....	2	0	0
Wound infection { Deep.....	0	0	0
Superficial.....	1	1	0
Operative deaths.....	2	0	0

of the subsequent stage for a few days. Two patients died as a direct result of the operation and will be discussed along with the late deaths.

### RESULTS

The results following thoracoplasty are presented in table 7.

One of the patients in the 40 to 49 year age group has been eliminated from these figures because it was impossible to locate him for check-up. The rest of the patients have all been followed for periods of one to seven years by repeated examination of concentrated sputum specimens, occasional guinea pig inoculations and by chest X-ray films. Twenty-one of the 29 patients alive have been

TABLE 7  
*Results—one to seven years follow-up*

	40-49 YEARS 19 CASES	50-59 YEARS 8 CASES	60-65 YEARS 4 CASES	TOTAL 31 CASES
	Number	Number	Number	Number
Arrested—able to work.....	13	6	3	22
Improved.....	4	2	0	6
Dead.....	2	0	1	3
Sputum conversion.....	14	6	3	23

followed for more than a year and were arrested and working when last seen. Seven were classified as improved. This includes 2 patients who are undergoing further surgical collapse and one patient who is recovering from a tuberculous infection of the opposite chest wall which she had prior to thoracoplasty. Her sputum has remained negative for the past year. The other 4 patients in this group of improved cases still have an occasional positive sputum but are able to work and get along fairly well. Two patients in this group had one- and three-stage thoracoplasties, respectively. More surgery is indicated but has been refused. Two of the patients died within three weeks of the operation and have been classed as operative deaths. One patient died several months postoperatively from progressive pulmonary tuberculosis despite three posterior stages, one antero-lateral and one revision. His sputum never became negative.

In listing the results of sputum conversion the 2 operative deaths have been omitted. This gives 23 conversions out of 29 patients, or 79 per cent. Two of the remaining 6 refused further surgery and 2 patients are awaiting further surgery.

There are 6 deaths in the entire series. These are shown in table 8. Two were operative deaths which occurred in women in their early forties. Both were due to right heart failure and occurred in patients who had initial vital capacities of less than 1,100 cc. One patient died ten months after his final stage which had failed to halt the progress of his disease. There were 3 deaths due to other causes. One woman died of cerebral hemorrhage at the age of 61, seven years after the arrest of her tuberculosis. Another woman died from Addison's disease eighteen months after the arrest of her pulmonary tuberculosis, and a third patient died four and one-half years after operation from an unrelated abdominal condition. During these years he had been working full-time and was free of symptoms.

The results on the 32 cases just presented, when compared with those reported by Dolley, Jones and Paxton (6) from fourteen different clinics on patients of all age groups, substantiate our views that patients over 40 stand the operation of

TABLE 8  
*Total deaths—6*

	40-49 YEARS 20 CASES	50-59 YEARS 8 CASES	60-65 YEARS 4 CASES	PER CENT FATALITY	
				Case	Stage
Operative mortality.....	2	0	0	6.25	2.47
Late deaths { Pulmonary tuberculosis...	0	0	1		
{ Other causes.....	2	1	0		
{ Extrapulmonary tubercu- losis.....	0	0	0		

thoracoplasty as well as younger ones and that as good results may be expected in them as in younger patients. Thus it would seem that thoracoplasty should be resorted to earlier in the course of the disease and used more frequently because of the increasing age of our tuberculous population and because so many of these older patients cannot be cured by the more conservative forms of collapse therapy.

#### CONCLUSIONS

The results following thoracoplasty for pulmonary tuberculosis in 32 patients between 40 and 65 years of age are presented. They compare favorably with those reported by Dolley, Jones and Paxton from fourteen different institutions in patients of all age groups. This substantiates our view that the age of the patient *per se* should not be the determining factor in the choice of therapy. Patients over 40 years were able to tolerate the operation and were benefited as much as those under that age. Thus it would seem that thoracoplasty should be used more frequently because of the increasing age of our tuberculous popula-

tion and because so many of these older patients cannot be cured by the more conservative methods of collapse therapy.

#### CONCLUSIONES

Preséntase el resultado consecutivo a la toracoplastia ejecutada por tuberculosis pulmonar en 32 enfermos de 40 a 65 años de edad, comparándose favorablemente con el comunicado por Dolley, Jones y Paxton para 14 distintas instituciones en enfermos de todas edades. Esto comprueba la opinión de los A. A., de que la edad del enfermo no debe ser *per se* el factor determinante en la selección de la terapéutica. Los enfermos de más de 40 años toleraron la operación y se beneficiaron lo mismo que los de menos edad. Parece, pues, que debe usarse la toracoplastia más frecuentemente debido a irse elevando la edad de la población tuberculosa y a no poderse curar muchos de estos enfermos de mayor edad con las técnicas más conservadoras de la colapsoterapia.

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# ARTIFICIAL PNEUMOTHORAX AND PNEUMONOLYSIS

## Results in 100 Patients

W. J. BRANDAY<sup>1</sup>

This paper describes the results of treatment of 100 patients in whom artificial pneumothorax was induced and who were found to require section of adhesions in order to effect a good collapse. In nearly three-quarters of the patients bilateral disease was present and in 27 of them collapse of both lungs was necessary. On these 100 patients, 162 operations were performed and in 4 patients the phrenic nerve was crushed in addition to the pneumothorax. The instrument used was the Jacobaeus thoracoscope with separate cannula for the cautery.

The Island of Jamaica, in which this work was performed, has an area of about 4,200 square miles and a population of about 1,230,000, nearly all of whom are of the colored race; there are a few thousand white persons and some thousands of East Indians and Chinese. The great majority of the population lives in very poor economic circumstances; nearly all are employed as laborers or servants of some kind and depend entirely on their work for the necessities of life.

The Island has a well developed medical service, the primary object of which is to provide medical care for those in the lowest income groups. In Kingston, there is a hospital of about 500 beds, with complete laboratory and X-ray facilities; in the rural areas, there are 20 district hospitals, varying in size from 10 to 200 beds. There are health departments in all parishes of the Island, each in the charge of a health officer, and there are specialist medical officers in charge of island-wide programs for the control of tuberculosis, malaria, venereal diseases and yaws. The capital city is Kingston, the population of which is over 200,000.

The present plan of control of tuberculosis was advised by Dr. Opie of the Rockefeller Foundation in 1927. The number of notified cases has fallen from 1,453 in 1936 to 1,165 in 1942; during the same years, deaths decreased from 1,083 to 960; during 1943, a rise of about 11 per cent occurred, probably due to war conditions, but figures for the year 1944 suggest that there will be a return to the 1942 level. This decline in morbidity and mortality is more encouraging than it appears, as it has taken place during years in which the facilities for the treatment and finding of cases have greatly increased; public health nurses are much more numerous than they were ten years ago, and the building of the King George V Jubilee Memorial Sanatorium, in 1940, and of wards attached to country hospitals have been an excellent advertisement for tuberculosis work, and have probably persuaded many patients with tuberculosis to attend for examination, who otherwise would have died without ever having been diagnosed. The total number of beds now available for tuberculosis in the Island is just over 600, of which about 350 are in Kingston.

The object of this paper is to try to indicate the results which may be expected in a group of patients treated by ambulatory pneumothorax, all of whom had adhesions which required section. Nearly all were of the colored race and appeared to have little resistance to tuberculosis. Their economic position was exceedingly

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poor and they could not afford to cease work for more than a few days. Obviously, this was a most unfavorable group of patients, many of whom could not be expected to benefit from any form of treatment. But there is a group in whom the outlook is even worse, and that is the group in whom artificial pneumothorax is induced and terminated after the first X-ray examination after induction, because it is then clear that treatment will be ineffective.

All cases in this series have now been under observation for over three years, and it is possible that some of those who now appear to be improving will relapse and die, but even so the results will compare favorably with carefully selected groups who were in far better economic circumstances and had the immense advantage of rigid sanatorium treatment. These results also indicate that attempts to treat this type of patient by collapse measures might be worth while, and they do not support statistical studies, such as those by Drolet (1), which suggest that collapse therapy does not alter the case fatality of tuberculosis, because all types of cases are included in his statistics, even those in which such treatment might be expected to make the patient worse.

Treatment of the patients in this series was undertaken in the manner described because no other treatment was possible on account of the inadequate facilities for hospitalization and the economic position of the great majority of the patients. No doubt, a certain number was actually made worse by treatment, but at least an equal number was benefited. Since the prognosis without treatment was hopeless, the work was performed for the sake of the small number who improved. In his book on pneumothorax treatment, Rafferty (2) states on page 174: "If the alternative to mass ambulatory pneumothorax is no treatment and no isolation, then there can be no argument as to the wisdom of choosing the former." The public health value of the conversion of the sputum from positive to negative in a considerable number of cases, even if only for a short time during which they may be educated in those new habits which will help to reduce the danger of infection of their contacts who are always numerous and intimate, was an important consideration, as emphasized by Tice (3).

#### SELECTION OF CASES

In selecting patients, pneumothorax was induced in many in whom it could not be considered the treatment of choice; it would have been better to keep the patient in bed for some weeks to allow some of the acute collateral inflammatory reaction to subside before beginning treatment. But advice to these patients that they should do this was a counsel of perfection which very few could follow; nearly all would promise but, as they were unable to do so, they would return at the end of the appointed time more ill than at their former visit. All patients treated by pneumothorax, in whom adhesions were found which required section, were included in this series; even those cases who appeared on X-ray examination to be inoperable, and were found to be so by thoracoscopy, were included as failures. The results in this group cannot, therefore, demonstrate the effects of artificial pneumothorax therapy in a carefully selected group, such as that described in the British Medical Journal of August, 1944 (4), but these

data offer some evidence of what results may be expected in a most unfavorable group of ambulatory patients treated by artificial pneumothorax and pneumonolysis. A final opinion as to the outcome of treatment in these cases cannot yet be expressed, as they have not been followed-up for a sufficiently long time.

For comparison with this series, the results obtained in 200 selected cases described in the paper quoted above (4) are given, though the two groups are not completely comparable. The cases in the latter group had been followed-up for five years, and all underwent a strict course of sanatorium regimen, whereas the present series have been followed-up for only three years, and not more than 10 per cent were in hospital or sanatorium for more than a few days. The two groups are compared in table 1.

TABLE 1

NUMBER OF CASES	DURATION OF OBSERVATION	NUMBER WITH BILATERAL COLLAPSE	ALIVE	DEAD	SPUTUM		SATISFACTORY COLLAPSE		
					Neg.	Pos.	Alive	Working	Per cent of Total
198 (BMJ)	5 years	Not stated	133	65	138	60	69	56	28
100 (This series)	3 years	27	61	39	42	58	34	28	28

## ECONOMIC POSITION

The majority of the patients were laborers or domestic servants; there were a few carpenters, tailors, shoemakers, clerks and dressmakers. Nearly all had no resources whatsoever on which they could fall back when their earning power was reduced or failed. Not more than 20 per cent could afford to cease work for more than a few days and continue to buy enough food while at rest. They were, therefore, forced either to go hungry or return to work, and they usually chose the latter with consequent damage to health. The majority could purchase only the minimum quantities of the cheapest foods and, therefore, suffered from malnutrition; the proteins, vitamins and mineral salts were particularly deficient. The home conditions were very bad; overcrowding was the rule and good clothing and comfort of every kind were wanting. It was useless to advise them to rest because they could not do so and continue to live; they nearly always promised to do so, and no doubt would if they could, but the result in 8 or 9 of every 10 patients was that they returned at the end of the period advised, confessing that they had been unable to rest, and suffering from more extensive disease than was found on their previous visit.

The number of illegitimate children born is very high; in the Corporate Area, in 1944, the total number of births was 5,489 of which nearly 70 per cent were illegitimate. In a large majority of cases, the fathers contribute nothing towards the maintenance of the children unless they are forced to do so by order of a court of law. Most of the children are brought up by the mothers without the assistance of the fathers.

## HOSPITALIZATION

Only a few of the patients in this series could afford to cease work for more than a week for the purpose of having the adhesions cut; the arrangement in the majority of cases was for the patient to enter the hospital on the day of operation and to leave five or six days later, in order to return to work after an absence of one week. This short period of rest in bed could not be expected to have any lasting effect on the case fatality. The small number who enjoyed longer periods of hospitalization, up to two or three months, appeared to live longer and maintain fair health than those who could not remain in hospital for this time. This was suggested by comparison of this series with a series of 100 consecutive cases of an even more unfavorable type, in whom artificial pneumothorax was so inefficient that it was abandoned after being maintained for only a few weeks, and no attempt to divide adhesions was made (table 2).

TABLE 2

CROTT	APPARENTLY WELL	PROGNOSIS		DEATHS
		Fair/Doubtful	Poor	
1 (January to July, 1941) (Pneumo- thorax abandoned as ineffective)	21	8	10	61
2 (Present series)	34	13	14	39

## TYPE OF DISEASE

The type of case most frequently seen was one in which the disease was far advanced and often bilateral and in which X-ray examination showed that the infiltration was characterized by extensive collateral reaction, indicating its acute nature; cavities were common and multiple cavities were not rare. Only 10 patients in this series had no cavity. In the far advanced group, only one case did not have a cavity. The classification used in this series is that of the National Tuberculosis Association. For comparison with this series, the classification of the last 100 cases seen at the Clinic in Kingston during the latter months of 1944 was as follows: far advanced, 69; moderately advanced, 23; minimal, 1; pleurisy with effusion, 7. It is common to find that patients who resemble in general appearance, and in the extent and type of disease revealed by X-ray, respond very differently to the infection and to treatment. Since nearly all roentgenograms are taken on paper, reproductions cannot be made satisfactorily and cases, therefore, cannot be illustrated.

## RACE

Two patients appeared to be white and 3 Chinese; the remainder were colored and varied from light brown, almost white, to black. The numbers are too small to warrant any conclusion, but it is worth remarking that one of the white patients is now dead and the other very ill. The outlook in 2 of 3 Chinese patients, all young women, is poor. Nearly all those who are doing well are,



therefore, of the colored race, but there is no excess of those of light color over those who are very dark.

### SEX

It will be seen from table 3 that 68 of the cases were female and 32 were males; no complete explanation of this unusual preponderance of the female sex can be given, but it is possible that two factors operate: (a) the females attend more regularly for their treatment and encourage efforts to convert an unsatisfactory type of collapse to a good type by operation, and (b) females are less active than males, and cases do not become hopeless so quickly, and treatment is, therefore, continued, though the final case fatality rate is the same.

For comparison with this series, of the 100 patients in whom artificial pneumothorax was induced prior to the beginning of this series, 50 per cent were females.

### AGE

The age distribution, given in table 3, is remarkable for the large number of persons under the age of 20, with a consequent decrease of those in the third decade. Of the 23 patients under 20, only 5 remain alive, and the prognosis is good in only one of these.

In table 3 cases are classified by stage of disease, age groups and sex. The numbers of deaths and survivors to date, the end of December, 1945, are given.

TABLE 3

STAGE OF DISEASE		AGE GROUPS				MALE	FEMALE	DEAD	ALIVE
		Under 20	20 to 29	30 to 39	40 and over				
Moderately advanced.....	45	11	23	7	4	12	33	14	31
Far advanced.....	55	12	27	11	5	20	35	25	30
Total.....	100	23	50	18	9	32	68	39	61

Of the 45 with moderately advanced disease, 31, or 70 per cent, remained alive, whereas of 55 far advanced cases, only 30, or 54 per cent, remained alive after the same length of time had elapsed. Of the 68 females in the series, 43 remained alive, whereas of the 32 males, 18 remained alive. Of the 43 females who remained alive, the outlook is good with persistently negative or no sputum in 23 cases, whereas of the 18 males who remain alive, the outlook is good in 11 cases. These figures are too small for statistical analysis, but they do not offer any evidence that there will be any difference in the rates of recovery between the two sexes.

### RESULTS OF OPERATIONS

In table 4 the result of operation is related to stage of disease and presence or absence of cavitation. In table 5 the completeness of section of the adhesions is

related to sputum conversion, survival and prognosis. Sputum has been examined by smear only, in the majority of cases, but several examinations are reported before the patient is classified as negative. In a few cases sputum has been examined by culture. Patients whose sputum is negative as a rule and positive occasionally are classified as positive; 2 or 3 of these have been included in the group of "Prognosis Favorable;" on the other hand, 2 patients in whom the lung is totally collapsed as a result of a spontaneous pneumothorax and empyema, even though the patient is apparently well and may be working, have been included in the unfavorable group.

Table 4 shows the frequency of cavitation in this series. Of the 36 cases in the moderately advanced group in which cavities were present, 21, or 60 per cent,

TABLE 4

STAGE OF DISEASE		TECHNICALLY EFFICIENT = 52			TECHNICALLY INEFFICIENT = 48		
		No Cavity	Cavity Closed	Cavity Open	No Cavity	Cavity Closed	Cavity Open
Moderately advanced....	45	5	14	5	4	7	10
Far advanced.....	55	1	18	9	0	13	14
	100	6	32	14	4	20	24

TABLE 5

RESULT OF OPERATION		SPUTUM		DEAD	ALIVE	
		Positive	Negative		Prognosis Favorable	Prognosis Unfavorable
Technically efficient.....	52	24	28	22	19	13
Technically inefficient.....	48	34	14	17	11	18
	100	58	42	39	30*	31

\* Incl. 4 treated by thoracoplasty and one by pneumoperitoneum.

of the cavities were closed by operation. In the far advanced group the proportion is nearly the same, suggesting that the operation was equally successful in the two groups in so far as the closure of cavities is concerned. But table 5 shows that those cases in which the operation is classed as technically efficient more frequently converted positive sputum to negative, with consequent improvement in prognosis. Thus, of the 52 cases in this group, 54 per cent are classed as negative, and in 40 per cent the prognosis is considered favorable. Corresponding figures in the technically inefficient group are 30 and 27 per cent, respectively. It should be noted that, of the 11 patients in this group in whom the prognosis was considered favorable, 5 had attained negative sputum by means of other treatment, namely thoracoplasty and pneumoperitoneum.

These 5 patients could not be included to indicate the results of treatment by artificial pneumothorax and pneumonolysis.

Adhesions varied from simple cords and bands which were easily and quickly divided to very complex and dense masses; some of the latter type were divided in one, two or three stages. No record was kept of the time taken for operation or of the area cauterized, but complications appeared more common and severe after section of the larger and more complex adhesions than in the simpler types.

Severe bleeding was not encountered in any of the 162 operations; in 3 or 4 cases bleeding occurred which was easily controlled by application of the cautery. The writer does not agree with the opinion expressed by the authors of the paper in the *British Medical Journal* (4) that "Adhesions to the mesial thoracic wall below the level of the clavicle are in most cases without effect on the course of the pneumothorax." In this series and in about 300 cases subsequently operated on, the course of the pneumothorax and the final outlook of the cases appeared to be more favorable in those in which the apex could be completely freed so that on X-ray films it was seen to lie at the level of the seventh or eighth posterior rib.

In the 27 patients in whom bilateral pneumothorax was necessary, section of adhesions was required in 9 cases on both sides. Dyspnea was sometimes so severe that operation had to be postponed until sufficient expansion of the contralateral lung had taken place; in other cases, in which no obvious difference could be discovered, no dyspnea at all was experienced, and it was felt that nervous apprehension of the patient played a most important part in dyspnea in many patients. The writer has since performed over 300 more pneumonolyses, in many of which bilateral collapse existed, and he still feels that apprehension plays an important rôle in a large number of patients in whom dyspnea is marked.

#### COMPLICATIONS

In table 6 the complications which were observed are listed in relation to the stage of the disease.

TABLE 6

STAGE OF DISEASE		COMPLICATIONS AFTER OPERATIONS				
		Effusion	Empyema	Spontaneous Pneumo- thorax	Contralateral Spread	
					Controlled	Progressed
Moderately advanced.....	45	18	4	2	3	6
Far advanced.....	55	17	8	2	3	9
	100	35	12	4	6	15

The incidence of complications of all kinds was the same in the two groups, but the incidence of the more serious complications was rather higher in the far advanced group than in the moderately advanced. As already stated, severe complications appeared to be related to the extent and complexity of the adhesions. The number who died or in whom the outlook is unfavorable is greater in the group in which efficient section of the adhesions was impossible than in the group in which division was complete.

Examination of the pus was not undertaken in cases in which spontaneous

pneumothorax appeared to be the cause of the empyema; in 3 other cases in which the pus was examined, culture was reported as sterile after three weeks and the infection was therefore presumed to be tuberculous.

#### DEATHS

Of the 100 patients in this series, 39 have died up to the end of December, 1915. One death occurred from each of the following causes: massive hemorrhage, anoxia, meningitis, probably tuberculous; in all other cases death appeared to be due to extension of disease and toxemia. It is worth remarking that 22 patients, in whom operation was technically efficient, died as a result of extension of disease, caused by persistently patent cavities, or of toxemia due to empyema, which was caused by a spontaneous pneumothorax in 4 cases.

#### SUMMARY AND CONCLUSIONS

1. The results are given of treatment of 100 patients by artificial pneumothorax, in whom section of adhesions was required in order to effect efficient collapse.
2. All cases were ambulant during the greater part of treatment; very few stayed in hospital more than a few days or weeks for operation, and nearly all continued to work.
3. Nearly all were in poor economic circumstances, able to afford the bare necessities of life and quite unable to obtain extra nourishment and rest.
4. Individual resistance appeared to be a most important factor in favorable progress and to depend on the economic position of the patient.
5. The type of cases was most unfavorable; treatment could not be expected often to be successful, as disease was extensive, often exudative with little evidence of fibrosis.
6. Efficiency of collapse appeared to be the factor in treatment which exerted the most decided influence on the outcome of the case.
7. Treatment of this group of patients appears to have been worth while in spite of the unfavorable type of disease and inability of patients to cease work on account of their economic circumstances.

#### SUMARIO Y CONCLUSIONES

1. Preséntase el resultado obtenido con el neumotórax terapéutico en 100 enfermos, en los que fué necesario resecar las adherencias a fin de obtener un colapso efectivo.
2. Todos los casos fueron ambulantes durante la mayor parte del tratamiento, muy pocos permanecieron en el hospital más de algunos días o semanas para la operación, y casi todos continuaron trabajando.
3. Casi todos se encontraban en malas condiciones económicas, y apenas podían costearse la vida, faltándoles los medios para obtener alimento y reposo complementarios.
4. La resistencia individual fué aparentemente un factor de la mayor importancia en el desenlace favorable, enlazándose con la posición económica del enfermo dado.
5. El tipo de los casos era de lo más desfavorable; y a menudo no cabía esperar

que el tratamiento surtiera efecto, por ser la enfermedad extensa, frecuentemente exudativa y con pocos signos de fibrosis.

6. La eficacia del colapso pareció ser el factor terapéutico que ejerció el mayor influjo sobre la evolución del caso.

7. El tratamiento de este grupo de enfermos parece que valió la pena, a pesar del tipo desfavorable de la dolencia y de la incapacidad de los enfermos para abandonar su trabajo a causa de su situación económica.

#### *Acknowledgment*

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# TUBERCULOSIS SURVEY AMONG CHINESE STUDENTS<sup>1</sup>

R. TAK ENG<sup>2</sup>

The tuberculin test is one of the most practical and important armaments used by the tuberculosis worker in the prevention of tuberculosis. The tuberculin survey, followed by X-ray examination of the reactors, helps to obtain accurate statistics of cases of clinical tuberculosis; sources of infection are found through the examination of family and contacts; and, finally, it spreads knowledge of the newer methods of diagnosis of tuberculosis.

It was common knowledge in Hong Kong that the prevalence of tuberculosis was high among its general population. Some medical men ventured to say that infection was universal in adults. Such conclusions seemed justified by the weekly health reports of 200 odd new cases of tuberculosis and 100 or more deaths. We wanted to secure accurate figures regarding the prevalence of tuberculosis in Hong Kong through tuberculin surveys. The difficulties of doing such work among the masses, the great majority of whom still adhered to old Chinese herb medicine, were fully realized. Attention was, therefore, focussed on Chinese students in private schools. Tuberculin testing was done on as many students as were willing to submit to the test.

Since the average Chinese layman lacks fundamental knowledge of the newer scientific methods of handling tuberculosis, it was necessary to educate them in order to obtain the best possible coöperation. Each student in the schools examined was given a little pamphlet which explained briefly the innocuousness and importance of the tuberculin test followed by fluoroscopy and X-ray examination of the reactors for the detection of patients with tuberculosis. Teachers were asked to support this with pep-talks. Those who wished to be examined were required to sign a card, since the examinations were not compulsory. It was a pleasant surprise to see the enthusiasm and interest which the majority of students showed toward the survey. An average of 80 per cent of the student body of the 16 schools approached responded favorably. As the first dose 0.01 mg. Old Tuberculin was used and 0.1 mg. was given to those whose first test was negative. Eighty-five per cent gave a positive reaction to the first dose. The reactors were fluoroscoped and those found with any suspicious lesions were told to consult their family physician and have their chests X-rayed.

The youngest tested was 6 and the oldest 30 years of age.

Table 1 presents some interesting findings. It was appalling to learn that 77.9 per cent were infected already at the ages of 6 to 10. The percentage rose in each five-year group until it became universal at the ages of 26 to 30. The number of students in the highest age group is much too small to be of absolute value; however, one cannot discount the age groups of 16 to 25, in which 92.3 to 94.5 per cent of the students were found to be infected.

<sup>1</sup> The work of this study was done in May, 1940 to December, 1941, before the Japanese occupation.

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All students were encouraged to have a fluoroscopic examination, irrespective of whether they were tested or not, as well as the negative reactors. X-ray films were not taken because of lack of materials and funds. Fellows and Ordway (1, 2) of the Metropolitan Insurance Company, after years of experience with X-ray films and fluoroscopy of the Company's employees, concluded that fluoroscopic examination of the chest was about 90 per cent accurate as compared with X-ray films. We realize that some minimal lesions might have been missed. However, we were most gratified to have been able to detect the

TABLE 1  
*Results of tuberculin tests according to age groups and sex*

AGE.....	6-10		11-15		16-20		21-25		26-30		TOTAL
Sex.....	M	F	M	F	M	F	M	F	M	F	
Positive.....	301	209	1,287	796	1,342	442	77	27	17	17	4,515
Negative.....	79	66	204	102	96	53	4	2			606
Total tested.....	655		2,389		1,933		110		34		5,121
Total positive.....	510		2,083		1,784		104		34		4,515
Per cent positive.....	77.9		87.2		92.3		94.5		100		88.2

TABLE 2  
*Prevalence of clinical pulmonary tuberculosis according to age groups and sex*

AGE.....	6-10		11-15		16-20		21-25		26-30		TOTAL
Sex.....	M	F	M	F	M	F	M	F	M	F	
Minimal.....	4	7	19	9	47	10	1		1		98
Moderately advanced.....	1		2	4	12	3	1				23
Far advanced.....			1	1	1						3
Total.....	5	7	22	14	60	13	2		1		124
Total.....	12		36		73		2		1		124

obvious lesions and their bearers were subsequently X-rayed. We fluoroscoped 4,644 students and detected 124, or 2.3 per cent, with pulmonary tuberculosis.

Table 2 shows that most of the patients belonged to the age groups of 11 to 15 and 16 to 20, with 36 and 73 cases, respectively. It is interesting to note that the majority of lesions were minimal (98), while 23 were moderately advanced and only 3 patients had far advanced lesions. There were 7 cases of extra-pulmonary lesions (not included in table 2); namely, 2 with pleurisy with effusion, one with diaphragmatic pleurisy and 4 with tuberculosis of the spine. Thus, a total of 131 (2.8 per cent) cases of tuberculosis were detected among 4,651 students examined.

Tuberculin tests were not done on the teachers, but most of them were fluoroscoped. Eleven cases of pulmonary tuberculosis were discovered; 6 had minimal, 2 moderately and 3 far advanced lesions.

Compared to similar surveys in U. S. A. and Canada, the prevalence of tuberculosis found in our study is very high. However, this is not surprising when one considers the progressive and extensive antituberculosis programs and the high economic and social standards in Canada and the United States. Finally, the population of Hong Kong had increased to three times its normal in the three years proceeding our survey. Refugees had flocked in from various parts of China, making proper housing, nutrition and sanitation difficult. With the strenuous efforts at prevention, undertaken by the local League and the Department of Health, one may look forward to much improvement in the future.

#### SUMMARY AND CONCLUSION.

1. Tuberculin surveys, followed by fluoroscopy and radiography, were conducted in 16 Chinese private schools in Hong Kong.

2. A total of 5,234 students were tested with 0.01 mg. OT and the negative reactors were retested with 0.1 mg. OT.

3. A positive reaction was observed in 4,515, or 88.2 per cent.

4. In the age group 6 to 10, 77.9 per cent were positive; and the infection rate increased in each five-year group, reaching more than 90 per cent in the ages above 16.

5. A total of 4,651 students were fluoroscoped and 131, or 2.8 per cent, cases of tuberculosis were found. Of these, 124 had pulmonary lesions, 2 had pleurisy with effusion, one had diaphragmatic pleurisy and 4 had tuberculosis of the spine.

6. An additional 11 cases of pulmonary tuberculosis were discovered among the teachers.

7. Tuberculosis infection is apparently universal among the Chinese population in Hong Kong and Canton; for the students examined were Cantonese. Hence, the tuberculin test may be eliminated in future work; only fluoroscopy and radiography are necessary for the detection of new cases of tuberculosis.

#### SUMARIO Y CONCLUSIONES

1. En 16 escuelas chinas particulares de Hong Kong lleváronse a cabo encuestas con tuberculina, seguidas de la roentgenoscopia y la radiografía.

2. A un total de 5,234 estudiantes se les comprobó con 0.01 mgm. de TA, recomprobándose a los negativos con 0.1 mgm. de TA.

3. En 4,515 (88.2 por ciento) se observó una reacción positiva.

4. En el grupo de 6-10 años de edad, 77.9 por ciento fueron positivos, y el índice de infección aumentó en cada grupo de cinco años, llegando a más de 90 por ciento al pasar de los 16 años de edad.

5. Se roentgenoscopió a un total de 4,651 estudiantes, descubriéndose 131 casos (2.8 por ciento) de tuberculosis. De éstos, 124 tenían lesiones pulmonares, 2 pleuresía con derrame, uno pleuresía diafragmática y 4 tuberculosis raquídea.

6. Entre los maestros descubriéronse 11 casos más de tuberculosis pulmonar.

7. La infección tuberculosa es aparentemente universal entre la población china de Hong Kong y Cantón, dado que los estudiantes examinados eran



cantoneses. Por esa razón puede eliminarse la prueba con la tuberculina en la labor futura, bastando con la roentgenoscopia y la radiografía para el descubrimiento de nuevos casos de tuberculosis.

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# TUBERCULOSIS IN CAPTIVE WILD BIRDS<sup>1</sup>

## Decrease of Its Incidence following a Change in Diets

HERBERT L. RATCLIFFE

Clinical and epidemiological studies have provided convincing evidence that resistance of mankind to tuberculosis is influenced, to a very great extent, by nutrition, but the dietary factors involved in this relationship have not been determined (1, 2). Experiments designed to investigate this problem usually have employed laboratory animals in which native resistance to the infection apparently is low at best. Thus, in them the progress of the disease may not be subject to significant modification. This suggestion is based on experience with tuberculosis in several species of subhuman primates. Perhaps a more advantageous approach to the problem might be had through a study of avian tuberculosis, since the following observations indicate that nutrition may play a decisive part in the resistance of several varieties of birds to this disease.

For many years tuberculosis has caused from 5 to 10 per cent of all deaths among birds in the Philadelphia Zoological Garden (3, 4). It has occurred in many different species and in widely separated exhibition areas. On the whole, however, this disease has been most common in a few of the better-represented taxonomic groups.

The exhibition periods of tuberculous birds (life spans after arrival in the Garden) have varied from less than one year to more than ten years. Therefore some infections are believed to have been imported, while others apparently have originated in the Garden, and could have developed through contact with either imported or endogenous cases of the disease.

In 1935 diets for many species of birds and mammals were changed in order to compensate for certain apparent deficiencies (5). During the following decade the incidence of avian tuberculosis has distinctly decreased. This report contains an analysis of mortality records for ten years before and ten years after diets were changed. From this an attempt will be made to estimate the influence of nutrition upon resistance of birds to tuberculosis.

### MATERIAL

In the period of twenty years covered by this study, over 3,000 birds have died in the Philadelphia Zoological Garden. All of them were examined postmortem and no specimen was listed as tuberculous unless lesions were characteristic. Diagnosis was supported by histological sections from approximately one-half of the infected birds as well as by cultures from 50 of them. All organisms isolated proved to be the avian strain of *Mycobacterium tuberculosis*.

<sup>1</sup> From the Penrose Research Laboratory of the Zoological Society of Philadelphia and the Department of Pathology of the University of Pennsylvania, Philadelphia, Pennsylvania.

The bird collection has contained representatives of twenty-seven Orders during the period of this study. Tuberculosis has occurred among fifteen of these groups; but in eleven of them the number of specimens has been too small or the infection too sporadic for detailed analysis. Thus, while some attention will be given to the occurrence of tuberculosis in the entire bird collection, the records of four Orders in which the disease has been most common will be considered more completely. These four Orders are: (1) the *Columbiformes* (doves and pigeons), (2) the *Galliformes* (pheasants and quail), (3) the *Psittaciformes* (parrots, etc.) and (4) the *Anseriformes* (ducks and geese).

These groups have made up about one-half of the bird collection, and more than half of all cases of tuberculosis were found among them. With one exception, which will be mentioned, each group has been exhibited within definitely restricted areas so that infection in one could not easily have spread to another. Thus, with one exception, the occurrence of tuberculosis in each group may be treated as an independent phenomenon.

*Cages:* Until 1937 the majority of the *Psittaciformes* were exhibited in small cages accommodating 2 or 3 birds. The fronts and backs of these cages were made of wire bars. The sides were sheet metal. In 1927 these birds were moved to larger quarters, where from 4 to 10 specimens could be exhibited conveniently in a single cage. These cages are constructed of open wire bars on a cement base with a painted plaster back. Actual contact with birds in adjoining cages is possible and there is free passage of air through the cage block. Cages for the *Columbiformes* are duplicates of those just described.

With few exceptions, the *Galliformes* have occupied partially shaded, wire-enclosed, outdoor pens, with floors of packed dirt and clay. Wooden shelters completely shade about one-tenth of the floor space. Cleaning has been limited to the frequent removal of obvious debris and the resurfacing of floors at intervals of about six months. Rarely are more than 6 birds exhibited in any one pen.

The majority of the *Anseriformes* have occupied one large pond through which there is a continuous flow of water. At least one-half of this enclosure is exposed to sunlight and less than one-half of the area is above water level.

A small number of anserine birds, never more than 20 at a time, made up part of a mixed exhibit in an indoor "flight" cage. This cage is constructed of wire on a cement base, approximately 20 by 30 feet. In the floor there is a centrally placed shallow pool, fed by a fountain of rough stone. Since 1936 both ends of the floor have been partially covered with peat moss. In this cage with the ducks and geese there have been an approximately equal number of *Ralliformes* (coots and gallinules) and *Lariformes* (gulls) and smaller numbers of other types of birds. This has been the only mixed group in which tuberculosis occurred. The infection has been limited to the *Ralliformes* and anserine birds.

#### DIETS

The original diets for birds of these four Orders were composed chiefly of whole and cracked grains, supplemented by fresh fruits and vegetables and by crushed oyster shell or other sources of minerals. Foods were mixed and distributed by the personnel in charge of the exhibition groups.

Equal parts of cracked corn and wheat screenings made up the larger part of the food for the *Columbiformes*, the *Galliformes*, and the *Anseriformes*, but the *Anseriformes* also received small quantities of ground meat and fish. A mixture of sunflower seed, hemp seed and millet seed, in which the first-named contributed about 75 per cent of the whole, was fed to the *Psittaciformes*. In the flight cage the grain mixtures, ground fish, chopped fish and ground meat were provided in separate dishes to accommodate the many varieties of birds.

Since 1935 all of these birds have received at least 70 per cent of their intake from a mixed ration composed of finely ground foodstuffs, compounded in bulk by mechanical means and fed as a stiff mash. Fresh fruits and vegetables have been supplementary foods (5). The mixed ration contains ground whole grains, legume meals, milk products, yeast and meat. By dry weight it is estimated to supply 20 to 25 per cent protein, 5 to 6 per cent fat, 40 to 45 per cent carbohydrate and 4 to 5 per cent minerals. With the supplementary foods it has sustained satisfactory growth and reproduction in a variety of mammals and birds.

## RESULTS

This bird collection and its subdivisions have undergone continuous but irregular changes as deaths occurred and replacements were purchased. During parts of both decades replacements fell well below losses. It is possible that

TABLE 1

*Frequency of tuberculosis among the bird collection in the Philadelphia Zoological Garden during periods of ten years before and ten years after a change in diets*

YEAR	STOCK	DEATHS	DEATH RATE	TUBERCULOSIS DEATHS	TPM*	YEAR	STOCK	DEATHS	DEATH RATE	TUBERCULOSIS DEATHS	TPM*
1926	1,282	281	21.9	20	7.5	1936	996	149	14.9	8	3.8
1927	1,271	276	21.7	22		1937	1,058	131	12.4	3	
1928	1,215	262	21.5	18	8.8	1938	1,226	179	14.6	19	8.7
1929	1,177	225	19.1	25		1939	1,094	189	17.3	13	
1930	1,261	246	19.5	25	8.5	1940	1,031	99	9.6	12	9.6
1931	1,165	203	17.9	14		1941	966	77	8.0	5	
1932	1,111	186	16.7	23	17.5	1942	960	84	8.8	7	5.6
1933	1,043	155	14.8	37		1943	857	129	15.0	5	
1934	952	151	15.7	17	12.3	1944	717	102	14.2	1	1.4
1935	1,033	141	13.6	19		1945	607	99	16.2	2	
Avg.....	1,151	213	18.5	22.0		Avg.....	951	123	12.9	7.5	

\* Tuberculosis Proportionate Mortality—deaths from tuberculosis as a percentage of all deaths, calculated by two-year intervals.

decreases in the size of the exhibition groups could have reduced the chances for the development of contact infections, and restricted replacements could have reduced the number of imported infections. Since the number of infections and the number of birds associated with them are a measure of the exposure to tuberculosis, these variations must be considered in relation to changes in the incidence of the disease.

Before considering the incidence of tuberculosis in the groups in which it has been most prevalent, the records of the entire collection will be reviewed. These are summarized in table 1, which shows: (1) the number of birds exhibited, (2) the number of deaths, (3) the death rate, (4) deaths from tuberculosis and (5) the tuberculosis proportionate mortality calculated for intervals of two years (6). Although feeding practices were changed during May and June, 1935, methods were not stabilized for some months. Therefore, in this table January 1, 1936 is taken as the dividing point. More accurate division does not seem to be demanded either by the study or by the character of tuberculosis in birds.

During the first decade the number of birds exhibited each year varied from over 1,200 to below 1,000. The decrease in the stock reflects the economic conditions of the early 1930's. It was accompanied by a decrease in the death rate from all causes, but losses from tuberculosis were not definitely affected. For two years following the change in diets, however, deaths from tuberculosis dropped to well below former levels. But with increased purchases of birds during 1937 and 1938, losses from the disease became more frequent and, for the next three years, almost equalled the average rate for the ten years prior to the change in feeding. As will be seen later, however, this increase in tuberculosis may be accounted for by imported infections. Since the outbreak of the war in 1939, the stock has again decreased (because of lack of importations) and the death rate also dropped for a time, but the drop in tuberculosis after 1940 seems to have been much greater than can be explained by the small stock exhibited and the lower death rate.

In the first decade the average number of birds exhibited each year was 1,151, with 21.7 deaths from tuberculosis, or 1.79 per cent of the stock. From 1936 through 1945 the stock averaged 951 birds, with 7.5 deaths from tuberculosis per year, or 0.79 per cent. These differences are magnified if records for the six years (1940-1945), when replacements were greatly limited, are compared with those for the period from 1930 through 1935, when replacements to the collection also were restricted. From 1930 through 1935 the stock of birds averaged 1,094, with 26 deaths from tuberculosis per year, or 2.36 per cent of the stock. From 1940 through 1945 an average of 875 birds have been exhibited. During the second period of six years, deaths from tuberculosis were 4.5 per year, or 0.51 per cent.

Application of the chi-square test to these records suggests that this decrease in the incidence of tuberculosis is considerably greater than might be expected from chance variation of material. The value of chi-square has been calculated from the number of nontuberculosis and tuberculosis deaths before and after the diets were changed, in the formula for a four-fold table (7). This computation gives 12 as the value of chi-square, which is equivalent to a probability of less

than 1 in 1,000 that this drop in the frequency of tuberculosis could have resulted from a chance selection of specimens.

This pattern of change in the incidence of tuberculosis in the whole collection also has been followed by two of the four Orders, in which the infection was

TABLE 2

*Frequency of tuberculosis in four orders of birds exhibited at the Philadelphia Zoological Garden for ten years before and ten years after a change of diets*

YEAR	Columbiformes (DOVES AND PIGEONS)				Galliformes (PHILANTHS AND QUAIL)				Psittaciformes (PARROTS, LORIES)				Anseriformes (DUCKS AND GEESE)			
	Deaths				Deaths				Deaths				Deaths			
	Stock	Total	Tuber- culosis	TPM*	Stock	Total	Tuber- culosis	TPM*	Stock	Total	Tuber- culosis	TPM*	Stock	Total	Tuber- culosis	TPM*
1925	51	4	1	55.0	79	27	6	23.0	135	40	1	3.5	270	18	2	15.0
1927	55	5	4		78	29	7		133	44	2		277	22	4	
1928	57	10	7		55	30	3		120	39	3		273	16	2	
1929	48	12	8	65.0	55	28	6	15.0	145	39	2	6.4	308	22	2	10.6
1930	43	11	6		74	17	3		150	36	2		251	14	5	
1931	31	3	3		70	19	4		145	27	2		255	21	1	
1932	33	3	2	70.0	74	10	6	54.0	111	23	2	14.8	262	20	5	18.6
1933	39	4	3		73	25	13		89	24	5		239	13	3	
1934	38	3	3		79	14	6		86	17	1		240	17	5	
1935	40	3	0	50.0	59	21	2	22.0	93	19	8	25.0	245	23	4	22.5
Avg.....	43	5.8	3.9		79	21.8	5.6		111	30.8	2.8		268	18.6	3.3	
1936	42	1	0	0	76	12	1	4.1	88	28	3	5.0	252	12	2	7.0
1937	52	0	0		103	36	1		91	32	0		290	17	0	
1938	54	3	2		95	49	6		89	37	1		323	19	5	
1939	32	2	0	40.0	116	23	4	16.0	62	10	0	2.1	243	14	3	24.2
1940	28	2	0		115	14	5		67	10	1		227	9	1	
1941	23	0	0		115	17	3		85	12	0		219	61	2	
1942	22	2	0	0	105	19	1	26.0	95	15	0	4.5	211	10	4	4.3
1943	26	3	0		93	21	1		99	18	1		208	33	3	
1944	24	2	0		74	18	0		99	15	0		191	12	0	
1945	24	3	0	0	66	8	0	5.0	95	22	0	3.0	196	19	1	16.3
Avg.....	32	1.8	0.2		95	20.8	2.2		87	19.9	0.6		236	20.6	2.1	

Annual changes in stock represent losses by deaths, sales, or exchanges as balanced, more or less, by replacements.

\* Tuberculosis Proportionate Mortality—deaths from tuberculosis as a percentage of all deaths calculated by two-year intervals.

most common, but in the others the decrease in deaths from the disease was much more abrupt. The records for these groups are shown in table 2. This table contains the number of birds exhibited, deaths from all causes and deaths from tuberculosis in each year. Tuberculosis proportionate mortality is also given, being calculated for intervals of two years.

In table 2, records for the *Anseriformes* include all deaths in this group.

Tuberculosis has been relatively rare among the part of this group which was exhibited on the pond, while among anserine birds in the flight cage the disease accounted for approximately 50 per cent of all deaths. Subtracting these infections from the total does not materially change the percentage decrease in tuberculosis after the change in diets. However, in applying the chi-square test only the records of anserine birds dying on the pond have been used.

The records given in table 2 show that, among the *Galliformes* and *Anseriformes*, deaths from tuberculosis varied from year to year in much the same way as in the collection as a whole. Among the *Columbiformes* and *Psittaciformes*, however, the change in the incidence of the disease was more abrupt. To some extent these differences are paralleled by rates of replacements for the groups. Thus it may be suggested that the changes in the frequency of tuberculosis as a cause of death have been influenced more by size of the group and its replacements than by nutrition. This possibility will be explored further after the changes in frequency have been considered in terms of "tuberculosis proportionate mortality."

The ratio of all deaths to deaths from tuberculosis has been termed "tuberculosis proportionate mortality" and used as a means of estimating the degree of improvement achieved in the control of tuberculosis among population groups (6). For the present material these ratios have been calculated by intervals of two years in order to reduce irregularities in the curves. This does not appear to change the values materially and it is an aid to presentation. The curves of these ratios for the collection as a whole, and for the four Orders of birds whose records have been presented in table 2, are shown in chart 1.

These curves are closely parallel through both decades, and emphasize the greater frequency of tuberculosis among birds of the groups listed in table 2. The upward trend of the ratios in the first decade reflects largely a falling death rate rather than any great increase in frequency of deaths from tuberculosis. However, the marked drop in both curves immediately following the change in diets reflects an actual decrease in tuberculosis below earlier levels, but this was increased by a slight rise in total deaths. Subsequent elevation of the curves reflect increases in numbers of infections as well as a falling death rate.

These values for the ratio of all deaths to deaths from tuberculosis suggest that nutrition has increased resistance to the spread of the disease. And values of this ratio for three of the four Orders of birds, whose composite ratios are shown in chart 1, also support this suggestion. The ratios for tuberculosis proportionate mortality among the *Anseriformes*, however, give a much more erratic curve than those of the other groups and do not fall convincingly in the second decade.

Judgment of these records in terms of tuberculosis proportionate mortality probably cannot be so definite as when this method is applied to human population groups. Among mankind tuberculosis is more a disease of young adults, whereas all evidence suggests that resistance of these birds does not change within the age groups which have been examined. Moreover, causes of death are not so well established as for mankind. Before diets were changed mal-

nutrition was a major factor in mortality. This has been eliminated by the new diets, but improved condition of the birds has increased losses through group conflicts and accidents of mating and breeding. To these must also be added an increasing number of deaths caused by ageing processes. However, the death rate during the second decade has been appreciably lower, but, as shown by the tuberculosis proportionate mortality, the decrease in tuberculosis in the col-

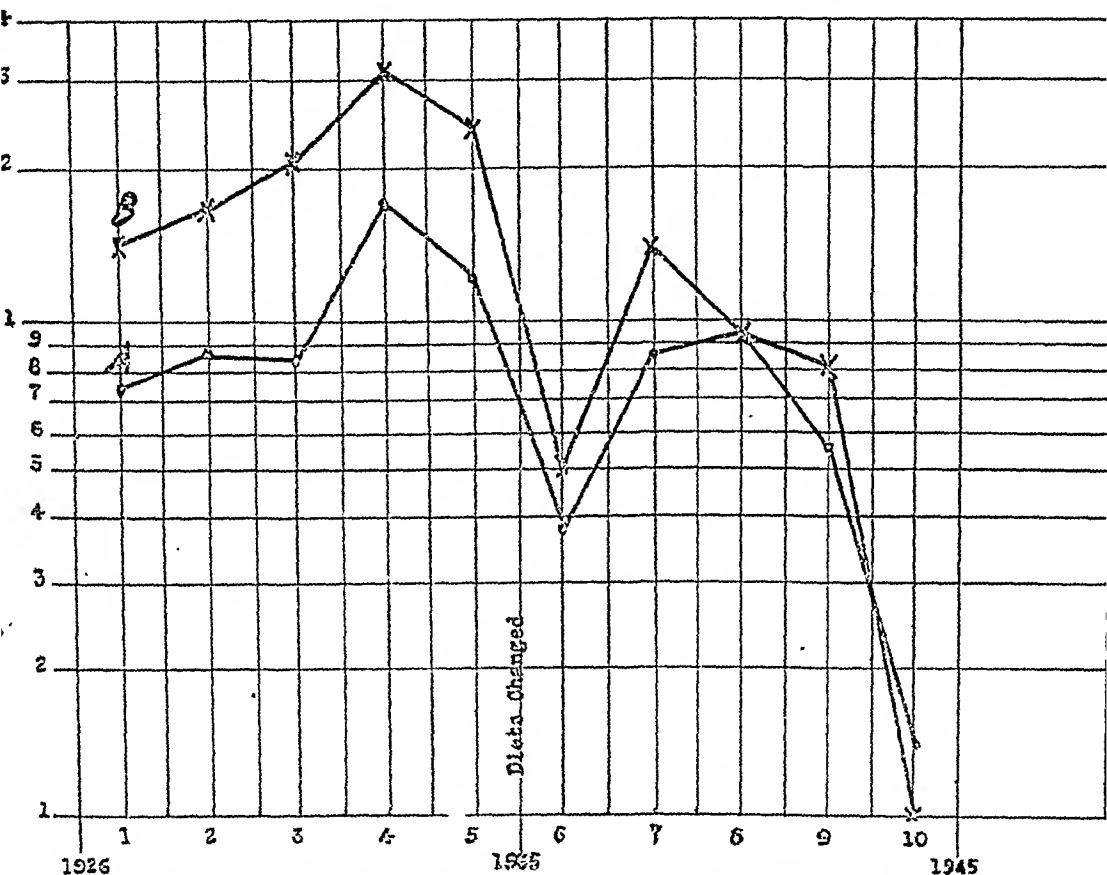


CHART 1. Tuberculosis proportionate mortality among birds exhibited and dying in the Philadelphia Zoological Garden from 1926 through 1945, calculated by intervals of two years. Curve A represents values for table 1. Curve B is a composite of table 2.

lection as a whole and in three of four Orders of birds has been greater than the decline in death rate.

Application of the chi-square test to these decreases in the incidence of tuberculosis among the four Orders of birds listed in table 2, by using the number of nontuberculous and tuberculous deaths during each decade, in the formula for a four-fold table, gives the following values: *Columbiformes* 15, *Galliformes* 16, *Psittaciformes* 5.97 and *Anseriformes* 3.60. The larger values of chi-square are equivalent to probabilities of less than 0.001 that selection influenced the results. The value for the records of *Psittaciformes* equals a probability of ap-



proximately 0.02, but that for the *Anseriformes* is somewhat greater and so may not represent a significant decrease in the frequency of tuberculosis.

This comparison of the frequency of tuberculosis by eli-square demands that each group have had a comparable degree of exposure to the infection before and after diets were changed. From table 2 it is evident that no group had an equal exposure in terms of total infections. But if imported infections continued to be introduced and endogenous infections did not develop, then resistance must have been increased.

Following the change in diets there was a distinct decrease in the number of infections among older birds of these groups, except the *Anseriformes*. The 2 cases in *Columbiformes* in 1938 were birds that had been on exhibition for over seven years. Only 4 of the deaths from tuberculosis in the *Galliformes* involved birds that had lived over six years and these died within four years after diets were improved. Likewise the 3 psittacine birds which died of tuberculosis within two years after foods were changed had been on exhibition for over six years. Thus, an analysis of deaths according to exhibition periods may aid in estimating the number of imported and endogenous infections which developed in each decade, and so provide a better evaluation of results than the methods which have been used. This analysis also permits a judgment of the influence of replacements and of size of groups upon the incidence of the disease.

Table 3 contains a summary of replacements, the numbers exhibited and of the cases of tuberculosis among birds of different age groups in each Order shown in table 2, and adds records for *Ralliformes*, among which the occurrence of the disease has been associated with their contact with certain of the anserine birds. Age groups are measured by exhibition periods. Replacements are given as totals for each decade. Numbers exhibited are the sums of replacements added to the number of each Order that was on hand at the beginning of the period of observation. Deaths are separated by yearly intervals up to six years.

For present purposes I have assumed that the duration of tuberculosis in birds of the Orders *Columbiformes*, *Galliformes* and *Ralliformes* might not be greater than three to four years. For the *Psittaciformes* and *Anseriformes* life expectancy after infection has been placed at four to five years. These intervals are based upon available estimates of the duration of the disease in chickens and domesticated ducks (8). Possibly these periods are too long and may exaggerate the number of imported infections, but this error would apply equally to observations during both decades.

Table 3 shows that replacements for the *Columbiformes*, the *Psittaciformes*, the *Ralliformes* and number of specimens on exhibition after 1935 were about one-half as great as in the first decade. Replacements for the *Galliformes* and the *Anseriformes*, as well as totals under observation, were essentially equal in both decades.

In all groups, except the *Anseriformes*, deaths from tuberculosis within the periods assumed to represent the life expectancy of imported infections accounted for one-half or more of all losses from the disease before 1936. During the second decade this has been true of only the *Galliformes* and the *Ralliformes*.

*Columbiformes* and psittacine birds received as replacements since 1935 have been peculiarly free of tuberculosis. Only one bird in the two groups died of the disease within less than five years after arrival.

In contrast to these groups, the *Galliformes* had 18 deaths from tuberculosis within four years of arrival during the second decade. This compares with 29 during the first half of the twenty-year period. Comparison of the distribution of these tuberculous deaths, by exhibition periods, shows a sharp separation between the infection in old and young birds after 1935. This suggests that some of the deaths under four years in the first period may have been endogenous infections. If the assumed life-span of tuberculous *Galliformes*, under the in-

TABLE 3

*Replacements, totals exhibited (stock) and deaths by years from less than one to more than six, for ten years before and ten years after a change in diets*

1926-1935	REPLACEMENTS	STOCK	DEATHS															
			Under 1 yr.		1-2 yr.		2-3 yr.		3-4 yr.		4-5 yr.		5-6 yr.		Over 6 yr.		Totals	
			Nontuber- culous	Tuber- culous	Nontuber- culous	Tuber- culous	Nontuber- culous	Tuber- culous	Nontuber- culous	Tuber- culous	Nontuber- culous	Tuber- culous	Nontuber- culous	Tuber- culous	Nontuber- culous	Tuber- culous	Nontuber- culous	Tuber- culous
<i>Columbiformes</i> ...	60	100	9	3	4	7	1	5	2	9	0	1	1	2	2	12	19	39
<i>Galliformes</i> .....	247	279	81	4	21	6	20	10	7	9	6	7	11	8	18	12	164	56
<i>Psittaciformes</i> ....	311	420	83	1	50	2	32	4	33	6	17	3	10	2	56	9	281	27
<i>Anseriformes</i> .....	293	511	34	2	9	2	12	1	7	2	4	1	6	2	81	23	153	33
<i>Ralliformes</i> .....	36	55	9	2	3	3	0	2	4	1	1	0	1	2	12	6	30	16
Totals.....	957	1,185	216	13	87	20	65	22	53	27	28	12	29	16	169	62	647	171
1936-1945																		
<i>Columbiformes</i> ...	28	69	2	0	1	0	3	0	0	0	1	0	1	0	8	2	16	2
<i>Galliformes</i> .....	246	305	50	1	30	8	23	7	26	2	12	0	12	0	33	4	186	22
<i>Psittaciformes</i> ....	163	241	39	0	26	1	17	0	25	0	15	0	11	2	60	3	193	6
<i>Anseriformes</i> .....	280	495	72	2	9	0	8	1	6	1	12	2	11	0	67	15	185	21
<i>Ralliformes</i> .....	14	20	5	1	0	1	0	1	1	0	0	1	2	0	3	2	11	6
Totals.....	731	1,121	168	4	66	10	51	9	58	3	40	3	37	2	171	26	591	57

fluence of the original diet, were taken to be three instead of four years, then this group has had approximately equal numbers of imported infections in each decade.

The records for the *Anseriformes*, as given in table 3, apply to the whole group. Dividing these according to exhibition areas shows that the part of the group on the pond received 258 replacements in the first decade and lost 19 birds from tuberculosis. Only 2 of these seem to have been imported infections. In the second decade, 280 replacements entered this part of the group. During this period there were 16 deaths from tuberculosis, 6 of which could have represented imported infections.

The mixed group in the flight cage received 71 replacements, 36 *Ralliformes* and 35 anserine birds, in the first decade and had 30 deaths from tuberculosis,

12 of which could have been imported infections. During the second decade anserine birds were not added to this group. Of those remaining, 5 have died of tuberculosis, the last in 1942. All of these had lived more than six years in this exhibit. Of the *Ralliformes* added to this group in the second decade, 3 died of tuberculosis within three years of arrival in the Garden.

The analysis of these records as given in table 3 suggests that resistance to tuberculosis varied little with age before 1935. The decrease in the frequency of the disease after diets were changed may be so interpreted. Perhaps this is the correct interpretation for, if improved feeding has increased resistance, this might well be best demonstrated by older birds.

#### DISCUSSION

Factors other than diet which might have influenced the incidence of tuberculosis among these birds would seem to be: (1) the degree of contamination of food and environment, (2) the frequency of infection among specimens added to the collection and (3) the frequency of contact between infected and uninfected birds within the exhibition areas.

If the original grain and seed mixtures had been contaminated and the new diet was not, then the decrease in tuberculosis could be accounted for without postulating increased resistance referable to improved nutrition. However, it must be granted that chances for contamination would increase with handling, and mixed food, composed of meals, should certainly be more likely to carry infection than whole or cracked grains. Therefore it seems reasonable to assume that contaminated food has not been a factor in these results.

Environmental infection should have been determined by efficiency of personnel and the frequency of tuberculosis among the birds. Both efficiency of personnel and frequency of infection are known to have decreased for a time after diets were changed. Perhaps it is not unreasonable to assume that these two factors balanced and so did not affect the changed incidence of tuberculosis.

With respect to frequency of contact, these records are believed to show that the *Galliformes*, during both decades, have had approximately equal grades of exposure to tuberculosis in terms of imported infections. All of the older birds that developed the disease since diets were changed could have been infected before 1935. None of the other groups have had a comparable grade of exposure. Nevertheless, the disappearance of tuberculosis among the *Columbiformes* and *Psittaciformes* has been a unique experience. Records of postmortem examination of these birds are continuous since 1905. Never before have they been free of tuberculosis. Thus, even though new infections were not introduced, past experience has shown that tuberculosis should have continued among them.

The pattern of the infection in the flight cage has been similar to that among the *Columbiformes* and the *Psittaciformes*. Here 3 infections apparently were introduced and 8 others developed after diets were changed. But, as judged by exhibition periods of the endogenous infections, there has been little or no spread of the disease since 1935. The disease has not been found in this cage since 1942, even though some 15 susceptible birds still survive from the first decade. This, too, has been a unique experience.

Among the anserine birds on the pond, tuberculosis apparently has been less dependent upon imported infections than in other exhibition areas. This group of birds has had a greater proportion of infection among older specimens than others. Possibly the duration of the disease in them has been underestimated, although the distribution of infection by age groups since 1935 does not support this opinion. In any event, the records of this group suggest that, thus far, increased resistance has not been demonstrated conclusively. The records of the other groups are believed to supply more convincing evidence that nutrition has been a decisive factor in reducing the spread of tuberculosis.

The most obvious difference between the old diets and the present system of feeding birds of the four Orders has been the amount and variety of protein supplied by the mixed ration. However, this ration also has added significant amounts of vitamins A and D and iodized salt to the diets, it has increased the intake of elements of the vitamin B complex, and has combined all nutrients into a well-mixed food.

The average condition of the birds fed the grain-mixtures did not suggest definite types of deficiencies. In general they were "unthrifty," the quality of the plumage often was poor, and usually they failed to breed when mated under suitable conditions. However, this was not a uniform response. Some specimens maintained satisfactory condition for ten years or more, but these were more than balanced by deaths within one or two years, a majority of which were attributed to nonspecific intestinal disease. These are indefinite abnormalities. Until they can be reproduced experimentally, it is useless to contend that specific deficiencies were represented. Nevertheless, these conditions have been corrected by the mixed ration.

Observations on tuberculosis and nutrition among many population groups suggest that the level of protein intake may be a critical factor in the incidence of disease (1, 2). A satisfactory experimental study of this relationship has not come to my attention, but there is abundant evidence that antibody formation and resistance to other infections are quickly impaired by deficient protein intake (9). On the other hand, improved feeding very quickly restores mammals to a high level of antibody formation (10). Thus, perhaps the prompt decrease in deaths from tuberculosis which followed the change in diets represents a real increase in resistance.

Possibly the level of dietary protein, as well as its quality, may have been the determining factor in the incidence of tuberculosis among these birds. However, the mixed group in the flight cage had abundant protein available to them. If physiological need influences taste, these foods should have been consumed in significant amounts (11). In view of this, perhaps it may be suggested that the relation of nutrition to resistance to tuberculosis does not depend entirely upon the quantity and quality of protein ingested, but upon a more complex interaction of several dietary factors.

#### SUMMARY

A change in the system of feeding at the Philadelphia Zoological Garden has been followed by a distinct decrease in the frequency of avian tuberculosis.

With the exception of a mixed lot of birds in an indoor flight cage, the disease has been most common among groups of birds whose food had consisted chiefly of whole or cracked grains. In the new diet grain has been replaced by a mixed ration. This has improved the quality and quantity of protein, it has increased elements of the vitamin B complex and has added vitamins A and D and iodized salt to the diets.

A comparison of replacements to the collection, totals exhibited and deaths during periods of ten years before and ten years after diets were changed shows that in some groups the drop in tuberculosis could have resulted from decreases in the number of imported infections. In other groups, however, all evidence suggests that resistance has been increased by improved nutrition, but the factors involved have not been determined.

#### SUMARIO

Un cambio introducido en el sistema de alimentación empleado en el Jardín Zoológico de Filadelfia ha ido seguido de una pronunciada disminución en la frecuencia de la tuberculosis aviaria. Exceptuado un grupo de aves mezcladas en una jaula de vuelos al interior, la enfermedad ha sido más frecuente en los grupos de aves cuya alimentación ha consistido principalmente en granos íntegros o rajados. En la nueva alimentación el grano ha sido reemplazado por una ración mixta, lo cual ha mejorado la cantidad y calidad de la proteína, aumentado los elementos del complejo vitamínico B y agregado vitaminas A y D y sal yodada al alimento.

Una comparación de los repuestos en la colección, los totales presentados y las muertes durante períodos de diez años antes y diez años después de cambiar la alimentación revela que, en algunos grupos, la baja de la tuberculosis puede deberse a disminución en el número de infecciones importadas. Sin embargo, en otros grupos, los datos sugieren que la resistencia ha aumentado por virtud de la mejor nutrición, pero no se han determinado los factores que intervienen.

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# AUTOLYTIC TUBERCULIN<sup>1,2</sup>

## Its Properties and the Significance of Its Mode of Formation

H. J. CORPER AND C. CLARK

Because of its vague nature and the confusion of its formation, the original tuberculin of Koch, Old Tuberculin, has been variously named, and its relation to tuberculosis during the succeeding decades has resulted in confusing and contradictory uses. Koch had some knowledge of its protein nature as it was derived from the tubercle bacilli during their growth, but the list of bacillary body tuberculins described attests to the ill defined character of its formation. Further confusion was added by the erroneous discovery of the presence of tuberculin both in the dead and living tuberculous patients. Thus it was only logical that tuberculin should be used first as a specific therapy for tuberculosis, then as a specific stimulant to the tuberculous focus, and finally as a diagnostic agent only. The confusion was further emphasized when the unification of specific tuberculo-immunity and specific tuberculin allergic hypersensitiveness was recognized (1). Finally, when intensive chemical studies by Long and Seibert (2) disclosed conclusively that the active constituent of Koch's Old Tuberculin was a tuberculoprotein, crystallizable and non-coagulable by heat and quantitatively precipitable by suitable protein precipitants, the way was paved for further information on this valuable biological product. Tuberculin is elaborated by the tubercle bacillus almost pure and readily recoverable in cultures grown on simple synthetic nonprotein media.

When it was more fully recognized that the elaboration of tuberculin (3) (tuberculoprotein) only began in appreciable amounts on simple nonprotein synthetic media after about one month at incubator temperature (37°C.) when the mammalian tubercle bacilli had attained maximum growth and that the young growing bacilli were practically free from inherent tuberculin (4), it became clear that the mechanism of liberation in the culture flask was in some way associated with possible death or injury of the bacillary bodies. It was thought this might possibly be associated with an enzymatic action, since heat at boiling water temperature and drastic chemical reagents capable of destroying vital processes completely prevented or destroyed the tuberculin-forming function of the tubercle bacilli. This led to the disclosure in 1943 (5) that tuberculin (tuberculoprotein) is produced by tubercle bacilli as the result of the action of the autolytic enzymes of the bacilli and that the enzymatic process resulting in tuberculin formation can proceed in the absence of bacillary viability—the process being one customarily referred to as autolysis. In 1943 and 1944 (6) it was pointed out that tubercle bacilli, grown on a simple nonprotein synthetic medium for one month and washed, autolyze (toluol treated) at incubator temperature at pH 7.0 to 8.0 to produce a maximum and highly potent biological

<sup>1</sup> From the Research Department, National Jewish Hospital, Denver, Colorado.

<sup>2</sup> This investigation was aided by a gift from Mr. and Mrs. Lothair S. Kohnstamm.

tuberculin (tuberculo-protein) within one week. The autolysis of tubercle bacilli occurs best at 37° C, and is practically completely retarded at 3° C. The autolysate obtained from tubercle bacilli is biologically identical in activity, as determined by anaphylactic and allergic tests, to the tuberculin (tuberculo-protein) obtained in the natural filtrate from growing these same bacilli on a nonprotein synthetic medium for over three months. This autolysate is free from contamination with extraneous constituents of the medium as well as foreign materials resulting from the growth of the bacilli. At that time it was suggested from the studies pursued on particle size that the tuberculin derived from autolysis of tubercle bacilli is not of uniform size but rather consists of a mixture of tuberculins varying in particle size from 480  $\mu\mu$  to 19 to 20  $\mu\mu$  in about 88 per cent of the tuberculin at least. It seemed likely that the potent enzymes of the bacilli act mainly intracellularly on the bacilli and probably are not liberated in sufficient concentration into the filtrate to be able to act upon the proteins of heat-killed or chemically killed bacilli. The liberation of the tuberculo-protein into the solution *in vitro* may also account for the difference, to some extent, between *in vitro* liberation of tuberculin and its absence *in vivo* by all evidence obtainable in man or animals.

The autolytic tuberculin which has been prepared with all aseptic precautions fulfills all the requirements for exacting sterility and is prepared free from all extraneous materials, being thus a pure uncontaminated bacillary product. When dried over phosphorous pentoxide *in vacuo*, it can be pulverized to a fine fine yellow powder which readily takes up water upon exposure to the air. About 10 per cent of its dry weight consists of the biologically active and chemically precipitable (with trichloroacetic acid) tuberculo-protein.

#### HYDROSCOPIC NATURE OF THE AUTOLYTIC TUBERCULIN

The following studies were pursued to gain a further insight into the physical and chemical nature of autolytic tuberculin and to compare it as completely as possible with other standard tuberculin materials, such as the purified protein derivative of Long and Seibert and Koch's OT. We especially wanted information on its adaptability for use in the transcutaneous tuberculin test (7, 8), for which it had been recommended as being particularly suited. For moisture absorption comparisons, a toluol prepared autolytic tuberculin was thoroughly dried over phosphorous pentoxide *in vacuo* and then weighed. A like amount of trichloroacetic acid precipitated tuberculo-protein, similarly dried over phosphorus pentoxide *in vacuo*, was weighed; and both were exposed to a moist atmosphere in a desiccator over water. At definite periods the receptacle and tuberculins were weighed carefully with the results given in table 1.

As to the hygroscopic nature of the autolytic tuberculin, 58 per cent of the moisture is absorbed in two days. The pure autolytic tuberculin is highly hygroscopic and is particularly suitable where moisture absorption is paramount in bringing the autolytic tuberculin into solution rapidly from the dry state without the necessity of adding water. Therefore, it is well adapted to the preparation of a material for transcutaneous testing with tuberculin, a feature which has been lacking in previously described pure tuberculins.

TABLE 1

*Absorption of moisture by dry autolytic tuberculin as compared with purified protein precipitate in air saturated with water vapor*

HOURS	PER CENT INCREASE IN MOISTURE CONTENT	
	Autolytic tuberculin (Dried over $P_2O_5$ )	Purified protein derivative (Dried over $P_2O_5$ )
Original moisture content	0	0
24	34.7	12.9
48	57.8	13.8
72	70.2	13.9
120	91.8*	13.9*

\* Upon return to air humidity conditions (in Denver, Colorado) at room temperature or at incubator temperature ( $37^{\circ} \text{C.}$ ), both the autolytic tuberculin and the purified protein derivative lost moisture; but the PPD lost it so much more rapidly that within one to two hours at 30 per cent humidity the moisture content of the PPD was less than 6 per cent, while that of the autolytic tuberculin remained above 80 per cent.

#### THE LIMITATIONS OF THE LIBERATION OF TUBERCULIN (TUBERCULOPROTEIN) IN THE PROCESS OF AGE FORMATION AND RECOVERY FROM THE MEDIUM

In the past the tuberculin whether prepared from broth medium cultures of tubercle bacilli or from nonprotein synthetic medium cultures, depended upon the growth of the bacilli and a prolonged residence in the incubator at  $37^{\circ} \text{C.}$  to permit the bacilli to liberate the tuberculin into the medium after good growth had been attained, and this usually varied in time from two to six or nine months. In order to gain an insight into the tuberculin formation as it pertains to other factors, such as the bacillary mass produced, an experiment was planned in which determinations were made at regular intervals after planting the bacilli on a simple synthetic nonprotein medium (Wong and Weinzirl (9)). The results are recorded in table 2.

The findings recorded in table 2 indicate maximum liberation of tuberculo-protein in about four months into the medium at  $37^{\circ} \text{C.}$  from about a maximum of a little over 5 g. (moisture-free weight) of bacillary mass. The total material (as approximated by charcoal absorption) liberated into the medium by the bacilli at  $37^{\circ} \text{C.}$ , and with a consequent loss in bacillary mass because of this, is about 40 per cent of the maximum bacillary moisture-free weight. The active tuberculin material liberated by the age culture process is practically all contained in the trichloroacetic acid protein precipitated material.

In the preparation of autolytic tuberculin and its preservation, use of heat or drastic physical procedures, the use of chemical reagents for precipitations or antiseptics as preservatives are rigidly avoided. The entire process, including filtrations and the bacillary forms used for preparation, is such that there is no danger involved at any time. This is not the case when a virulent strain of bacilli like H37 is used, which has been advocated and widely applied in the preparations of OT and purified protein derivatives. Also, except for precipitation test purposes of the product, trichloroacetic acid or other protein precipitants are not



used in preparing the autolytic tuberculin. Therefore, in order to note differences, possibly denaturing influences which can occur following the use of heat on tuberculin preparations, a series of tests was performed to determine, if possible, what differences are displayed following the use of these procedures.

TABLE 2

*The relation of bacillary mass to tuberculin (tuberculoprotein) in the age culture process*

INCUBATION TIME (37° C.)	pH	A: MOISTURE-FREE WEIGHT OF BACILLI IN GRAMS	B: WEIGHT IN GRAMS OF CHARCOAL ABSORBABLE SUBSTANCES*	TRICHLOROACETIC ACID PRECIPITABLE PROTEIN IN MILLIGRAMS†	TOTAL MOISTURE- FREE MATERIAL (GRAMS) A + B
0	7.0	0	0.3	0	0.3
1 month	7.0	2.4	0.5	6	2.9
2 months	6.8	4.2	0.8	107	5.0
3 months	6.0	4.7	1.0	100	5.7
4 months	5.7	4.4	1.5	153	5.9
6 months	5.7	3.6	1.9	176	5.5
8 months	5.6	3.3	1.9	150	5.2
10 months	5.6	3.4	2.0	145	5.4
12 months	5.5	2.7	2.0	168	4.7

\* To remove the bacilli, the entire bottle content (500 cc. culture medium) was filtered using a Seitz filter pad (weighed). For the charcoal absorption figures, about 200 cc. was treated with Darco charcoal and the absorbed material removed for weighing by treatment with a 50 per cent solution of isopropylamine, the latter being evaporated and the residue weighed.

† The figures were obtained by using the Seibert factor on the trichloroacetic acid precipitate measured in Hopkins tubes.

# *I. Results of chemical and biological analysis of autolytic tuberculin as compared with trichloroacetic acid precipitated protein in various process parts:*

## *A. Analysis of autolytic tuberculin (AT)*

Nitrogen content.....	5.82%
Ash content.....	19.9%
Biological activity.....	10.0%
(in equivalent to 1 mg. per cc. of tuberculoprotein in natural Seitz filtrate from culture of tubercle bacilli on a nonprotein medium)	
Trichloroacetic acid (10%) TCA precipitable material.....	15.7%
which contains as nitrogen.....	13.5%
Biological activity.....about .....	100.0%
There remained in the filtrate (FAT) after TCA precipitation, dried and extracted with ether, solids.....	77.0%
(loss of solids probably due to ether extraction)	
which contained as nitrogen.....	2.6%
Biological activity on this material was.....	0.0%
Tungstic acid (0.5%) precipitation of the above filtrate (FAT) yielded solids.....	5.81%
which contains as nitrogen.....	14.8%
With a biological activity.....	10.0%

Total tungstic acid (0.5%) precipitate of	
Autolytic tuberculin (AT).....	17.6%
which contains as nitrogen.....	14.6%

The above analyses indicate that trichloroacetic acid precipitation does not remove all biological reactive specific substance from the autolytic tuberculin. Lack of biological activity from the TCA filtrate led to overlooking of specific active substances previously.

B. The effect of heat and phenol on recovery of biologically active material from culture filtrates of tubercle bacilli. (These analyses were made on cultures of tubercle bacilli which had grown for over five months and were submitted to different treatment.)

1. Unheated culture normal Seitz filtrate.....	100 cc.
Trichloroacetic acid (10%) precipitate.....	0.126 g.
Nitrogen content.....	14.5%
Biological activity (approximately).....	80.0%
The filtrate from this TCA precipitation possessed no biological activity after drying and extracting with ether to remove TCA. Since ether extraction removes various materials, nitrogen determinations on this filtrate proved of no value.	

Tungstic acid (0.5%) precipitation of the TCA filtrate, however, yielded.....	0.038 g.
with nitrogen content equal.....	14.05%
Biological activity (approximately).....	1.0%

2. Heated (Arnold sterilization) culture Seitz filtrate.....	100 cc.
Trichloroacetic acid (10%) precipitate.....	0.094 g.
Nitrogen content.....	14.6%
Biological activity (approximately).....	80.0%
The filtrate from this TCA precipitation possessed no biological activity after drying and ether extraction to remove TCA. Therefore, nitrogen determination of no value.	

Tungstic acid (0.5%) precipitation of the TCA filtrate yielded, with nitrogen content equal.....	0.0037 g.
Biological activity (approximately).....	14.55%
	1.0%

3. Phenol treated Seitz filtrates from cultures of tubercle bacilli	
a. with 0.5% pure phenol added to above #1.....	100 cc.
Trichloroacetic acid (10%) precipitate.....	0.130 g.
Nitrogen content.....	14.05%
Biological activity (approximately).....	80.0%
The filtrate from this TCA precipitation possessed no biological activity after drying and ether extraction to remove TCA. Examination of filtrate, therefore, of no value.	

b. with 0.5% pure phenol added to #2.....	100 cc.
Trichloroacetic acid (10%) precipitate.....	0.0974 g.
Nitrogen content.....	14.0%
Biological activity (approximately).....	80.0%
Filtrate from TCA precipitation possessed no biological activity after drying and ether extraction.	

Note in above analyses B1 and 2 the larger amount of TCA precipitable material in the 1) unheated (0.126 g.) as compared with the 2) heated (0.094 g.) and also the larger amount of tungstic acid precipitable material in the filtrate from the TCA precipitation 1) unheated (0.0382 g.), as compared with the 2) heated (0.0037 g.). It was also noted that the heated solutions were far darker in color (probably due to disintegration of organic compounds by the heat).

The phenol apparently does not interfere with the biological activity, although the analyses would indicate an effect due to the addition of the phenol on the protein reflected in the lower nitrogen content of the TCA precipitate. Again, note a lowered amount of TCA precipitate from the heated 3b as compared with the 3a.

The foregoing findings and analytical data indicate that the trichloroacetic acid precipitates from normal Seitz filtrate, from phenolized (0.5 per cent) normal Seitz filtrate, from heated Seitz filtrate and from phenolized, heated Seitz filtrate had slightly less activity than equivalent amounts of normal Seitz filtrate (on a 1 mg. trichloroacetic acid precipitate basis).

Heating and phenolization had no effect on the biological activity of the preparations made from these filtrates as far as discernible.

Very little demonstrable biological activity remains in the filtrates after trichloroacetic acid precipitation of Seitz filtrate or autolytic tuberculin. This is due to the large dilutions by the remaining materials in these filtrates or by inhibition effects.

The tungstic acid precipitate from normal Seitz and autolytic tuberculin after trichloroacetic acid precipitation *have biological activity*. This indicates that trichloroacetic acid does not quantitatively precipitate all the biologically active material and far more active material remains in the filtrate from trichloroacetic acid precipitation of the unheated and unphenolized preparations (including both larger and smaller molecular specific materials).

#### THE RECOVERY OF TUBERCULIN (TUBERCULOPROTEIN) FROM CULTURES OF TUBERCLE BACILLI BY THE AGE PROCESS AND THE AUTOLYTIC PROCEDURE

Differences might exist between the tuberculin (tuberculo-protein) liberated during the slow age process and that produced by the autolytic process. The latter is more direct in that the bacilli evolved the tuberculin more rapidly and by a more direct process towards its liberation rather than leaving this to the age-time process which might result not only in loss of product but also to denaturation and degradation of the desired tuberculin product. In order to gain an insight into this, an experiment was planned in which the weight of bacillary

mass grown on a simple synthetic nonprotein medium (Wong-Weinzirl) was correlated at different periods following planting and incubation at 37° C. The

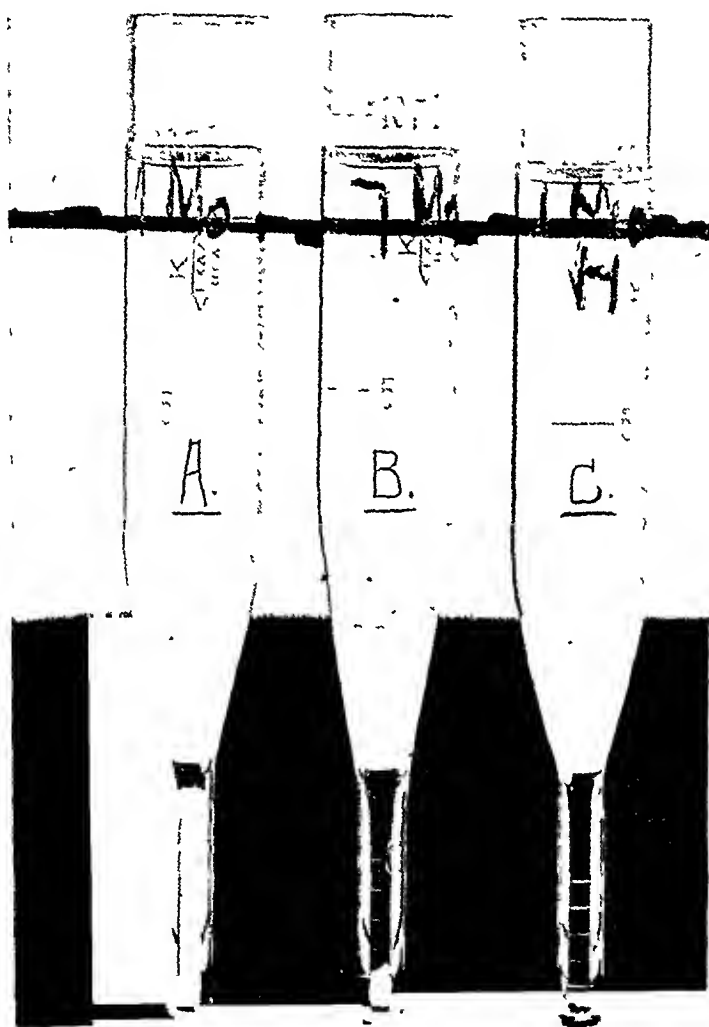


FIG. 1. Tuberculo-protein liberated by the autolysis of tubercle bacilli

A The trichloroacetic acid (TCA) precipitate from 0.10 g. of bacilli (moisture-free weight) grown for one month at 37° C. and then submitted to the autolytic process, and

B. from 0.18 g. of bacilli (moisture-free weight) grown for seven months at 37° C. and the bacilli then submitted to the autolytic process; and

C. from 0.11 g. bacilli (moisture-free weight) grown one month at 37° C., heated in an Arnold steam sterilizer, and the bacilli then submitted to the autolytic process.

Note the relative amounts of tuberculo-protein (as TCA precipitate) liberated—far more at one month than after seven months' incubation of the bacilli.

total mass was closely followed during the age process and during the autolytic process to discern the active tuberculin (tuberculo-protein) and other significant products. (See figure 1.) Although this experiment was performed in a number

of ways at various time intervals, it will suffice here to report the results at certain pertinent intervals in regard to the autolytic process and the preparation of autolytic tuberculin. As is customary in our laboratory, tubercle bacilli were planted on the surface of 500 cc. sterile Wong-Weinzirl medium, contained in screw cap one-liter narrow-mouth bottles chosen to reduce evaporation to a minimum at 37° C. for long periods of time. Planting, volume of liquid, incubation and all other procedures were standardized to avoid differences so far as possible. Likewise, all analytical methods were performed in a uniform comparable manner, suitable to accurate evaluation. All evaluations were made on the basis of the total mass of bacilli (moisture-free dry weight) and the products formed therefrom as reflected in the significant figures on a percentage basis. In individual comparative series, the same single strain of tubercle bacilli was used so no differences would arise on this basis. In most of these studies, the strain was an avirulent human tubercle bacillus which had been a stable organism in our laboratory for many decades. The results obtained from a one month old culture (at 37° C.) of avirulent human tubercle bacilli were as follows: the yield of bacillary mass determined as moisture-free bacilli (dried *in vacuo* over phosphorus pentoxide) was 2.08 g. (from 500 cc. original volume Wong-Weinzirl medium). The medium filtrate from these bacilli at one month contained 6 mg. of trichloroacetic acid precipitable protein (tuberculin). When submitted to toluene autolysis in distilled water with a few milligrams of sodium carbonate for one week at 37° C., these bacilli yielded 97.1 mg. of trichloroacetic acid precipitable protein and 1.044 g. of dry autolytic tuberculin; and the yield of autolytic tuberculin was about 50 per cent of the dry bacillary mass (moist bacilli were used for obtaining this autolytic tuberculin, however). A duplicate run with about the same amount of bacilli yielded 1.032 g. of autolytic tuberculin and the same amount of trichloroacetic acid precipitable protein as the above. The results obtained from a 200 day old culture at 37° C. of the same avirulent human tubercle bacilli planted on 500 cc. Wong-Weinzirl medium gave the following figures: The liquid medium filtrate from the bacilli contained 133 mg. of trichloroacetic acid precipitable protein at this time, and the moisture-free dry weight of the bacilli was 3.56 g. On the premise that the trichloroacetic acid precipitable protein (tuberculin) was 10 per cent of the material freed from the dried bacilli on the basis of autolytic tuberculin figures, this amount of material would be equivalent to 1.33 g. of bacillary mass (ten times the tuberculin weight), thus making the total amount equivalent to  $3.56 + 1.33 = 4.89$  g. moisture-free dry weight. On this basis, the age process formed tuberculin as the equivalent of autolytic tuberculin accounts for a liberation of 27.2 per cent. From the 3.56 g. of tubercle bacilli (determined as moisture-free bacilli) and autolyzed in the moist state with toluene at 37° C. for one week, a yield of 0.240 g. of autolytic tuberculin was obtained, or a yield of 6.7 per cent of the residual bacilli remaining after 200 days' incubation. This added to the 27.2 per cent of autolytic tuberculin equivalent accounted for in the medium resulting from filtration of the bacilli accounts for a total of 33.9 per cent of the total bacillary mass as figured.

The yield of tuberculoprotein (trichloroacetic acid precipitable protein) in the

autolytic tuberculin from the bacilli and remaining in them at 200 days was 21.3 mg., or 7 mg. per gram moisture-free residual bacilli as compared with 46.7 mg. per gram moisture-free bacilli found after one month's incubation at 37° C.

The duplicate run on the foregoing yielded about the same amount of residual bacilli at 200 days' incubation and about the same amount of autolytic tuberculin equivalent recovered from the medium filtrate; but the recovery of autolytic tuberculin from the residual bacilli after one week's incubation under toluol at 37° C. yielded only 16.2 mg. of trichloroacetic acid precipitable protein, or 4.5 mg. per gram residual moisture-free bacilli.

As a control on the liberation of tuberculin (tuberculo-protein), a one month old culture of tubercle bacilli was autoclaved for fifteen minutes at 17 lb. pressure (115° C.). The medium filtrate contained 42 mg. of trichloroacetic acid precipitable protein (tuberculin), while the bacillary mass consisted of 2.33 g. determined as moisture-free bacilli. The latter, the heat-killed bacilli, were suspended in distilled water and submitted to incubation at 37° C. for one week under toluol. From this, a filtrate was obtained containing 140 mg., weighed as moisture-free material with no perceptible trichloroacetic acid precipitable (tuberculin) material being evident. A duplicate run on a similar amount of bacilli yielded 129 mg. of moisture-free material (about 5.5 per cent of bacillary dry weight) and there was 1.3 mg. of trichloroacetic acid precipitable protein present.

In earlier studies we found that drying tubercle bacilli offered a ready method of preserving the bacilli for years at refrigerator temperature (10) without loss of viability.

In order to note whether drying of the bacillary mass interfered in any way with the efficient production of autolytic tuberculin, one month old (37° C. growth) cultures were dried over phosphorus pentoxide *in vacuo* and were then weighed and submitted to the regular procedure of suspending in distilled water with a trace of sodium carbonate under toluol for one week at incubator temperature. The results were as follows: the first test containing 1.90 g. of bacilli determined as moisture-free weight yielded 0.665 g. dry autolytic tuberculin and contained 51 mg. trichloroacetic acid precipitable protein tuberculin (tuberculo-protein), which was equal to about 35 per cent of the dry bacillary weight, and only 7.7 per cent of this (instead of the usual 10 per cent) consisted of tuberculo-protein. The duplicate test on 1.90 g. dry bacilli yielded 0.678 g. dry autolytic tuberculin containing 66 mg. tuberculin (tuberculo-protein—trichloroacetic acid precipitable protein) which was equal to about 35.7 per cent of the dry bacillary weight, and this gave a better percentage of trichloroacetic acid precipitable protein—9.7 per cent tuberculin (tuberculo-protein).

The foregoing experiments indicate that the bacillary mass from the one month old culture at 37° C. yields the largest amount of autolytic tuberculin to the extent that 50 per cent of the dry moisture-free bacillary weight is transformed by the autolytic process (with toluene) into autolytic tuberculin. This autolytic tuberculin contains about 10 per cent of its weight as trichloroacetic acid precipitable protein, which amounts to about 5 per cent of the bacillary dry weight as tuberculo-protein. With aging of the culture mass at incubator temperature to

the 200-day interval, there is an increase in the amount of tuberculin (tuberculo-protein) in solution in the nutrient medium, but the recovery is only approximately 27.2 per cent. Accordingly, the bacillary mass decreases in amount and, as a result, a correspondingly less amount of bacillary tuberculin remains in the residual tubercle bacilli which leads to a reduced amount recoverable by the autolytic (toluol) process. This approximates about 6.7 per cent at the 200-day interval. Thus the yield of autolytic tuberculin per gram bacillary mass recoverable after one month gradually becomes increasingly less as the incubation (37° C.) of the culture continues to the 200-day period. Heating at 100° C. of a one month old culture grown at 37° C. discloses the presence of a small amount of tuberculo-protein in the medium filtrate, but this heat also destroys the autolytic enzymes so that no further autolysis occurs. Therefore there is no additional liberation of tuberculo-protein by the bacilli either naturally or by applying the autolytic process.

Drying (*in vacuo*) of the viable bacillary mass to a moisture-free condition and subsequent suspension in distilled water under toluol and incubation at 37° C. results in a more restricted liberation of autolytic tuberculin to the extent that a yield of only 36 per cent autolytic tuberculin results. This would indicate that drying of the bacilli interferes either with the enzymatic autolytic process or so alters the bacilli that the formation of autolytic tuberculin (tuberculo-protein) is basically interfered with to some extent.

#### SUMMARY AND CONCLUSIONS

1. Autolytic tuberculin in the dry powder state is hygroscopic. When placed in a moist atmosphere over water, it rapidly absorbs about 35 per cent moisture in twenty-four hours and reaches over 90 per cent in 120 hours. Purified protein derivative tuberculin absorbs only about 14 per cent under the same conditions. When restored to air humidity conditions (about 30 per cent), both lose moisture; but, within one to two hours, the autolytic tuberculin retained over 80 per cent while the purified protein derivative retained less than 6 per cent. This hygroscopic property of autolytic tuberculin makes it highly suited to purposes of transcutaneous testing, a property absent from other standard tuberculins.

2. Trichloroacetic acid precipitates from normal Seitz filtrate, from phenolized (0.5 per cent) normal Seitz filtrate, from heated Seitz filtrate and from phenolized heated Seitz filtrate from cultures of tubercle bacilli possessed slightly less tuberculin activity than equivalent amounts of normal Seitz filtrate (on a 1 mg. trichloroacetic acid precipitate basis). Heating and phenolization had no discernible effect on the biological activity of the preparations made from these filtrates. Very little demonstrable biological activity remains in the filtrates after trichloroacetic acid precipitation of Seitz filtrates or autolytic tuberculin, caused largely by the dilutions from the remaining materials in these filtrates or by the presence of inhibition effects. The tungstic acid precipitate from normal Seitz and autolytic tuberculin after trichloroacetic acid precipitation possesses biological activity, indicating that trichloroacetic acid does not quantitatively precipitate all the biologically active material and far more active material re-

mains in the filtrate from trichloroacetic acid precipitation of the unheated and unphenolized preparations (including both larger and smaller molecular specific materials).

3. The bacillary mass from the one month old culture of tubercle bacilli at 37° C. yields the largest amount of autolytic tuberculin to the extent that 50 per cent of the dry bacillary weight is transformed into autolytic tuberculin. This contains about 10 per cent trichloroacetic acid precipitable protein by weight. With aging of the culture mass at incubator temperature (37° C.) to the 200-day interval, an increase is found in the amount of tuberculin in solution in the nutrient medium, but recovery is only approximately 27 per cent. Accordingly, the bacillary mass decreases in amount and, as a result, a correspondingly less amount of potential bacillary tuberculin occurs which leads to a reduced amount recoverable by the autolytic process applied to these bacilli. This approximates about 6.7 per cent at the 200-day interval.

Heating of a one month old culture at 100° C. and then incubating at 37° C. discloses no further autolysis of the bacilli and, therefore, no appreciable liberation of tuberculin.

However, drying *in vacuo* of the viable bacillary mass to a moisture-free condition, which serves to preserve the viability of the bacilli, results in a more restricted liberation of autolytic tuberculin—only 36 per cent instead of the 50 per cent from bacilli that had not been dried previously. The exact nature of this effect is not yet understood.

#### SUMARIO Y CONCLUSIONES

1. La tuberculina autolítica en forma de polvo seco es higroscópica. Colocada en una atmósfera húmeda sobre agua, absorbe rápidamente más o menos 35 por ciento de humedad en 24 horas y más de 90 por ciento en 120 horas. La tuberculina en forma de derivado proteínico purificado no absorbe más que aproximadamente 14 por ciento en condiciones idénticas. Cuando se reponen en las condiciones de la humedad atmosférica (aproximadamente 30 por ciento), ambas, pierden humedad, pero en término de una a dos horas, la tuberculina autolítica retuvo más de 80 por ciento, comparado con menos de 6 por ciento por el derivado proteínico purificado. Esta propiedad higroscópica de la tuberculina autolítica, que no poseen las otras tuberculinas aceptadas, la convierte en muy apropiada para la comprobación transcutánea.

2. Los precipitados con ácido tricloroacético del: filtrado de Seitz normal, filtrado de Seitz normal fenicado (0.5 por ciento), filtrado de Seitz calentado y filtrado de Seitz calentado y fenicado, de cultivos de bacilos tuberculosos, mostraron una actividad tuberculínica ligeramente menor que cantidades equivalentes del filtrado de Seitz normal (a base de 1 mgm. de precipitado con ácido tricloroacético). La calefacción y la fenicación no ejercieron efecto discernible sobre la actividad biológica de las preparaciones de dichos filtrados, restando muy poca actividad biológica ya en los filtrados de Seitz o en la tuberculina autolítica tras la precipitación con ácido tricloroacético, debido en gran parte a la dilución de las sustancias restantes o a la intervención de un efecto inhibitor.



El precipitado con ácido tungstico del filtrado de Seitz normal y de la tuberculina autolítica después de la precipitación con ácido tricloroacético posee actividad biológica, lo cual indica que el último ácido no precipita cuantitativamente todo el material biológicamente activo, restando sustancias mucho más activas en el filtrado precipitado con ácido tricloroacético de las preparaciones sin calentar ni fenicar (comprendiendo sustancias específicas de moléculas tanto grandes como pequeñas).

3. La masa bacilar derivada de un mes de cultivo de bacilos tuberculosos a 37°C. produce la cantidad máxima de tuberculina autolítica a tal punto que 50 por ciento del peso de los bacilos en seco se transforma en tuberculina autolítica, la cual a su vez contiene aproximadamente 10 por ciento de proteína precipitable con ácido tricloroacético en peso. Al envejecer la masa de cultivos a la temperatura de la estufa (37°C.) por un plazo de 200 días, obsérvese un aumento en la cantidad de tuberculina disuelta en el medio nutritivo, pero la recuperada no pasa aproximadamente de 27 por ciento. Por lo tanto, la cantidad de masa bacilar disminuye, y al mismo tiempo, la de tuberculina bacilar potencial, dando por resultado que, al aplicar a dichos bacilos el procedimiento autolítico, se obtiene una cantidad menor, que se aproxima a 6.7 por ciento a los 200 días.

La calefacción a 100°C. de un cultivo de un mes, seguida de la incubación a 37°C., no revela autólisis ulterior de los bacilos, ni tampoco, naturalmente, liberación apreciable de tuberculina.

No obstante, la desecación al vacío de la masa bacilar viable hasta un estado higroprivo, que sirve para conservar la viabilidad de los bacilos, da por resultado un desprendimiento más limitado de tuberculina autolítica: sólo 36 en vez del 50 por ciento de los bacilos que no se habían desecado antes. No se comprende aun exactamente la naturaleza de este efecto.

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# SOLITARY PULMONARY TUMOR

## Cyst-like Tumors Associated with Anomalies of Ribs

EDGAR WAYBURN<sup>1</sup>

During the course of a mass chest X-ray survey (35 mm.) of personnel in the U. S. Air Forces in Europe from April to September, 1945 (1) many conditions of the chest other than pulmonary tuberculosis were encountered among the 77,480 persons examined. Among these were 4 instances of a discrete solitary circumscribed radio-opaque shadow in the right lower lobe in asymptomatic, healthy, white men. Their ages ranged from 22 to 32. Three had had previous X-rays films of the chest within the preceding three years. Since none of them knew of the existence of the chest shadow before, one assumes that the shadow either was not present or was not noticed.

The tumors (table 1) measured 2.0 to 3.5 cm. in diameter and were located in the posterior portion of the right lower lobe just above or just below the crest of the dome of the diaphragm. One was medial, the others were centrally placed. In 3 of the cases there was associated with the pulmonary tumor an anomaly of a rib, including one left cervical rib and 2 bifid anterior endings of the right fourth rib. Investigations for periods up to ten days were made in U. S. Army General or Station Hospitals. No abnormality other than those mentioned was found.

The diagnosis is obscure. Inasmuch as all the tumors occur in asymptomatic, apparently healthy young men, they are probably benign. Surgical exploration did not seem justifiable in view of the lack of disturbed function. The pathognomonic roentgenological signs of chondroma (2, 3) and echinococcus cyst (4, 5) are lacking. During the course of a report on 2 benign spheroid pulmonary tumors, Brunn (6) commented on the need for a registry. One of his cases was a subacute granuloma, the other a myoma.

Tumors of the type reported here are rare. They are not mentioned in standard texts on neoplastic disease (7, 8). Recent reviews (9, 10) on solitary pulmonary tumors cite the fact that such lesions occur but list no cases. Among 23 cases of so-called solitary circumscribed tumors of the lung reported by Thornton, Adams and Bloch (10), only one, a hemangioma, was a benign tumor; 18 were malignant and 5 were of tuberculous origin. None of the cases resembled those published herein. Brahdy (11) has reported a round tumor, roentgenologically similar to those reported in this paper, at the base of the right lung behind the dome of the diaphragm. This tumor doubled its size in three years before it was removed. It was diagnosed pathologically as a fibroleiomyoma; there was no recurrence at the time of the report, six months later. Robbins (12) has reported 15 "bronchiogenic" cysts, some of which he considered to be congenital and some acquired. One group was discovered because of secondary infection which resulted in a picture simulating lung abscess or empyema with bronchial fistula. The others, like the cases in the present series, were incidental findings at roentgenological examination. He considered that the

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TABLE 1  
Summary of data on 4 solitary pulmonary tumors

CASE NUMBER	AGE	RESIDENCE	WEIGHT CHANGE	DESCRIPTION OF PULMONARY TUMOR	RIB ANOMALY	OTHER FINDINGS
1 WJW (figure 1)	32	New Jersey	Gain of 20 lbs. in three years	Discrete spheroid shadow 2.2 cm. in diameter in postero-central part of right lower lobe	Bifid anterior ending of right fourth rib	None
2 LMK (figures 2 and 3)	25	Iowa	Stationary	Discrete circumscribed shadow 2.5 cm. in diameter, flattened in superior - inferior axis in postero-lateral part of right lower lobe	None	None
3 RWK (figure 4)	22	Georgia	Loss of 7 lbs. in two and one-half years	Discrete spheroid shadow 2.0 cm. in diameter in postero-central part of right lower lobe	Bifid anterior ending of right fourth rib	None
4 CTR (figure 5)	25	Virginia	Gain of 22 lbs. in three and one-half years	Discrete spheroid shadow 3.5 cm. in diameter in postero-medial part of right lower lobe	Left cervical rib	None

most important radiological characteristic was a smooth, round or ovoid shadow without evidence of calcification or bone erosion. Additional evidence included attachment to the trachea or a bronchus. In some of his cases, due to a shift in the liquid or air composition of the contents, the mass showed changes in shape or opacity which would be unlikely in a solid tumor. These cases revealed no constant location or association with anomalies of bones.

The X-ray films of the present group of cases have been shown to a number of radiologists and physicians interested in diseases of the chest. Opinions as to

FIG. 1. (Top) Case 1  
FIG. 2. (Centre left) Case 2  
FIG. 3. (Centre right) Case 2  
FIG. 4. (Lower left) Case 3  
FIG. 5. (Lower right) Case 4



the nature of the tumors include bronchial cyst, pleural cyst, leiomyoma, semi-noma and chondroma. The first diagnosis was favored for the first 3 cases.

Although the data presented are scanty, several reasons justify the presentation of these tumors. Their occurrence in a routine mass survey of apparently healthy men is comparatively high. They show a remarkable similarity of location, all being in the posterior part of the right lower lung, with 3 out of 4 centrally placed. They have an extraordinary coincidence with rib anomalies. Statistical calculation of this association shows that it is extremely improbable as a chance event. It seems, therefore, most likely that the lesions in the lungs, like those in the bones, are of congenital origin.

#### SUMMARY

Four solitary spheroid pulmonary tumors, discovered in asymptomatic young men during the course of a mass radiographic survey of over 77,000 soldiers in the U. S. Army Air Forces in Europe, are reported. All the lesions were in the posterior portion of the right lower lobe. Three of the 4 were associated with congenital anomalies of the rib. They are considered to be bronchial cysts of congenital origin.

#### SUMARIO

Describense cuatro tumores pulmonares esferoideos solitarios descubiertos en jóvenes asintomáticos mientras se hacía una encuesta radiográfica en masa de más de 77,000 soldados de las Fuerzas de Aviación del Ejército de E. U. A. en Europa. Todas las lesiones radicaban en la porción posterior del lóbulo inferior derecho, y 3 de las 4 se asociaban con anomalías congénitas de las costillas. Estos tumores se consideran como quistes bronquiales de origen congénito.

#### *Acknowledgment*

I am indebted to Dr. Peter Kerley for his kind assistance.

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# BRONCHOLITHIASIS<sup>1</sup>

DANIEL W. ZAHN<sup>2</sup>

The symptom complex of broncholithiasis has received increasing attention in recent years. Until 1941 Anderson and MacKay (1) noted that only 26 cases had been reported in the English literature. Since that time, single cases have been reported by Evans and Cooper (2) and Rubinstein (3). Van Ordstrand, Moore and Harris (4) reported 2 cases, as did Zweifel (5). Tinney and Moersch (6) collected 28 cases from the files of the Mayo Clinic and Fox and Clerf (7) have recently described 10 additional cases of broncholithiasis.

The majority of patients seek medical attention because of (1) symptoms indicating bronchial obstruction, (2) the onset of hemoptysis and (3) the expectoration of calculi. In the first group the symptoms of cough, purulent expectoration, fever and chills lead to roentgenographic investigation which often reveals a collapsed lobe, nonspecific pneumonitis, suppurative pneumonia or lung abscess. A total of 71 cases of broncholithiasis has been reported in the literature. Of this number, 45 (63 per cent) have exhibited evidences of bronchial obstruction clinically and radiographically. It is interesting to note that, in 18 (40 per cent) of these latter cases, the pneumonitis cleared rapidly following the expectoration or bronchoscopic removal of the stone. In 2 instances the clinical and roentgenographic picture simulated bronchogenic carcinoma so closely that exploratory thoracotomy was performed (1, 8).

In many instances the bronchoscopist may be able to see the calculus protruding into the bronchial lumen. Indeed, in recent years bronchoscopy has been the principal method of diagnosis of this entity.

In the second group, hemoptysis may occur alone or may be associated with evidence of bronchial obstruction. In the 71 cases cited above, hemoptysis occurred in 50 (70 per cent) instances. In most of these cases it was associated with evidence of bronchial obstruction. Where hemoptysis is the only symptom the further investigation of the case usually includes bronchoscopy at which time the etiological agent, namely, bronchial calculus, is detected.

In the third group, the history of expectoration of calculi is often sufficient to make the diagnosis but corroborative evidence may be gained by bronchoscopy. Thus, 35 (49 per cent) of the above 71 cases gave a definite history of expectoration of calculi and in 29 of these the diagnosis was made by the history of stone-spitting alone.

## CASE REPORT

A 31 year old medical officer was perfectly well until the end of 1944 at which time he noted the onset of a mild, nonproductive cough. In February, 1945, he suffered a febrile illness characterized by malaise, fever and increased cough productive of small amounts of

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purulent sputum. At this time the officer examined his own sputum and noted many acid-fast bacilli on direct smear. On the following day the sputum was again positive on direct smear but thereafter daily sputa examinations were negative. During that week, his fever ranged from 100° to 102° F.; however, during the following two weeks he ran an afternoon temperature of 99.4° F. X-ray examination of the chest at this time was interpreted as normal.

Although still performing full duty, he continued to feel poorly and in May, 1945 he noted that he had lost 14 lbs. in weight during the preceding three months. At this time



FIG. 1



FIG. 2

FIG. 1. Chest X-ray film of January 13, 1944, which shows calcifications at right hilar region.

FIG. 2. Chest X-ray film of October 30, 1945, which reveals diminished number of calcifications at right hilar area as compared with figure 1.

he again suffered a febrile illness similar to the previous episode and characterized by fever, malaise and mild cough productive of a small amount of purulent sputum. An X-ray film of the chest was again interpreted as normal. Sputum examination, performed by the laboratory, was negative on smear. A guinea pig inoculated with this sputum was autopsied at the end of eight weeks. Examination showed lesions in the liver, lungs and right inguinal lymph nodes from which acid-fast bacilli were isolated.

He was hospitalized in June, 1945 and an extensive work-up was performed. Blood count, urinalysis and erythrocyte sedimentation rate were normal. Chest X-ray films,



including oblique views, were considered normal. Agglutination tests for typhoid, paratyphoid and undulant fever were negative. Bronchoscopy was performed at this time and no abnormalities were noted. Five sputa and three gastric washings were negative for tubercle bacilli on culture.

He was transferred to Fitzsimons General Hospital on September 16, 1945 for further study. His complaints were those of a mild cough productive of 4 to 8 cc. mucopurulent sputum daily and occasional dull substernal pain with cough. Wheezing was denied. Physical examination was within normal limits. Blood count, urinalysis and erythrocyte sedimentation rate were again normal. Three twenty-four-hour sputum concentrates were negative but thereafter two gastric washings and two sputa were positive on culture. A coccidioidin skin test 1:100 was negative, but a tuberculin skin test employing first strength PPD (0.000,02 mg.) elicited a two-plus response. Bronchoscopy was again negative and ear, nose and throat examination with special emphasis on the nasopharynx was negative.

At this time the patient was questioned more closely and he recalled that between February and August, 1945 he had expectorated about eight small, stony-hard greyish-white pieces of material varying in diameter from 2 to 5 mm. There was no pain, wheezing or hemoptysis during or following the expectoration of these stones. Unfortunately, none of these broncholiths were saved for pathological study.

Review of serial X-ray films from 1941 to the present time revealed the presence of a cluster of calcifications just below the right hilum in all films through 1944 (figure 1). The X-ray films of 1945 show a definite decrease in the number of calcifications in this area (figure 2).

The diagnosis in this case was based on (1) a definite history of expectoration of broncholiths, (2) the disappearance of calcified lesions as seen on serial X-ray films and (3) sputum positive for tubercle bacilli on smear and culture.

#### DISCUSSION

Considering the frequency of calcification in tuberculosis, it is rather surprising to note the low reported incidence of broncholithiasis. In over 5,000 cases of pulmonary tuberculosis observed by Stivelman (9) only one instance of broncholithiasis was noted. The experience at this Hospital has been similar. In over 4,000 cases of pulmonary tuberculosis, admitted to this institution in 1945, the case reported here represents the only instance of broncholithiasis.

The above case demonstrates in unequivocal fashion the potential dangers inherent in the so-called healed primary complex. It has been a much debated question as to whether calcified tuberculous lesions may harbor viable tubercle bacilli. Dejerene (10) in 1884 considered that a completely calcified lesion was non-infective. Griffith (11) observed that tuberculous lesions of long duration rarely, if ever, contain tubercle bacilli. Feldman and Baggenstoss (12) employed both culture and animal inoculation in 68 cases in which deaths were due to causes other than tuberculosis. The material was obtained from Ghon tubercles and hilar lymph nodes. Positive results were obtained in only one out of the 68 cases. They concluded that the lesions of the healed primary complex seldom contain viable tubercle bacilli and that, accordingly, endogenous reinfection is unlikely to occur from such lesions.

Conversely Pinner (13) pointed out in a discussion of the above contribution

(12) that active tuberculous lesions were not an infrequent finding in the lymph drainage between hilum and venous angle in the presence of completely calcified or ossified primary complexes. From these foci, he contended, reinfection may occur in the presence of completely healed primary complexes. The majority of investigators appear to agree with Pinner's conclusions. Rabinowitsch (14), using the guinea pig inoculation technique, studied the infectivity of calcified lymph nodes in 4 adults. In each instance positive results were obtained. Schmitz (15) similarly obtained positive results in 13 out of 28 cases. Opic and Aronson (16) found that, in 30 per cent of cases in which material from apparently healed lesions in the lungs and lymph nodes was injected into guinea pigs, tubercle bacilli could be demonstrated. Robertson (17), basing his results on morphological data, concluded that tuberculous lesions which have apparently healed may become clinically active after varying intervals of time.

Ghon (18) and Calmette (19) both believed that in the majority of cases the healing of a primary complex is incomplete and that viable tubercle bacilli can be demonstrated by guinea pig inoculation.

It is a striking feature of the case reported here that despite the presence of a positive sputum for almost a year, there has been no demonstrable evidence of endogenous reinfection (parenchymal involvement). This cannot be attributed to the small number of bacilli since several sputa were positive on direct smear. It must be concluded that this failure of the organism to produce demonstrable lesions is due to (1) high resistance of the host and/or (2) low virulence of the organism. Proof of the latter is in part afforded by the fact that the guinea pig inoculated with the patient's sputum, although exhibiting tuberculous lesions, did not die at the end of eight weeks.

The present case is unique in that it represents the only reported instance of broncholithiasis with positive sputum and no evidence of parenchymal involvement. The sequence of events probably stemmed from tuberculous involvement of the tracheobronchial and bronchopulmonary nodes as a result of a primary infection. These nodes in the process of healing became calcified. It is likely, however, that the nodes retained a caseous core in which were embedded viable tubercle bacilli. During this healing process the capsule of the node became adherent to the bronchus. At some later date an exacerbation of the specific periadenitis occurred which slowly involved the wall of the bronchus. Perforation of the bronchus then followed and was associated with the extrusion of the caseous core of the adjacent node into the bronchial lumen. The fact that the sputum remained positive over a period of almost a year suggests actual involvement of the bronchus itself by direct extension of the disease process: in other words, a condition akin to a tuberculous ulcer of the bronchus had developed.

In the ordinary case of tuberculous endobronchitis treatment is directed toward the feeding lesion, which in almost all instances is situated in the lung parenchyma. In this case, however, the situation is comparable to that of an isolated tuberculous endobronchitis without a demonstrable parenchymal lesion. Furthermore, the bronchoscopist was unable to see the lesion on two occasions,

thereby rendering impossible any form of topical therapy (for example with silver nitrate) which still has a large number of supporters. Although specific therapy cannot be based on the observations of previous workers a rationale may be devised using the broad principles from which present-day tuberculosis therapy has been evolved.

In his recent appraisal of strict bed-rest in the treatment of minimal tuberculosis, Bray (20) introduced the argument that, since endobronchial tuberculosis shows a natural tendency to heal and since the bronchi must move with respiration, it follows that strict rest is not essential for the healing of a tuberculous lesion. Myerson (21) has amply demonstrated this natural tendency for endobronchial tuberculosis to heal; certainly, this tendency can be greatly enhanced by the one form of therapy which over and over again has proved its worth, namely, rest. It cannot be denied that the bronchi undergo alterations in calibre and length during respiration but obviously these movements are at a minimum when the patient is on strict bed-rest. Therefore, it would seem that the best form of therapy in a case such as this would be to enhance this natural tendency for the endobronchial lesion to heal by the well recognized advantages of bed-rest.

#### SUMMARY

1. A patient with broncholithiasis with positive sputum and no demonstrable parenchymal lesion is reported; a discussion of the pathogenesis is presented.
2. The literature is reviewed with particular reference to the symptomatology of this condition.
3. The potential danger of the so-called healed primary complex is discussed.

#### SUMARIO

1. Descríbese un caso de broncolitiasis con esputo positivo y sin lesión parenquimatosa aparente, discutiéndose la patogenia.
2. Repásase la literatura con referencia particular a la semiología de este estado.
3. Discútese el peligro potencial que entraña el llamado complejo primario cicatrizado.

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## EDITORIAL

### Case-Finding in Tuberculosis

With the advent of new tools for the detection of pulmonary lesions has come a great surge of interest in case-finding in tuberculosis. The photofluorograph has provided a fairly accurate method of examining the lungs for evidence of this disease. The rapidity with which such examinations can be made, with little inconvenience to those examined, has resulted in large numbers being surveyed. Plans for even more extensive surveys are being developed. It is now possible to think in terms of examining the whole population in a period of not too many years.

Such plans are very good but it would seem wise to bear in mind that wholesale X-ray examination of the population is not the complete answer to the tuberculosis problem.

Without going into detail, almost everyone who has given the matter any study agrees that mass surveys will result in finding cases early and that this is desirable for obvious reasons. However, it must not be lost sight of that just finding evidence of a lesion in the lung by X-ray examination is but the beginning of the program. Is the technique employed adequate? Is the roentgenogram or fluorogram sufficiently clear to make a satisfactory interpretation possible? Next is accuracy of the interpretation; has it been made by an interpreter whose training and experience will minimize the possibility of error?

Granted that the technique and the interpretation are well done, there is the problem of explaining to the person whose examination has revealed possible trouble the nature of the situation sufficiently well to enlist his cooperation. Persuading him to submit to further examination and the following of medical advice as to treatment, if it is found necessary, is very difficult. In most instances the person has willingly submitted to examination, believing himself to be quite well and anyone who even suggests the contrary just cannot be right. There are, of course, some instances where the person immediately jumps to the conclusion that he is much sicker than he really is, but these are few compared with those who find it hard to believe there is anything wrong. To deal with this part of the program requires the patient understanding of the physician and nurse. Such interviewing may be done by persons of other experience or training, but preferably by a professionally trained person. Even under the best of conditions it is frequently disheartening to note how many of the early cases uncovered by surveys are lost entirely or great delay is experienced in getting their cooperation.

Not the least of the problems presented in providing for the proper follow-up is concerned with the facilities available for the treatment of the cases which may be found. It is conceivable that a demonstration in case-finding might be conducted in an area where adequate facilities do not exist, for the purpose of pointing out this inadequacy and thereby stimulating the responsible agencies to provide proper facilities as promptly as possible. Even though hospital or sanatorium beds may not be available, a program for utilizing beds in general

hospitals, supervising patients at home or otherwise providing for follow-up of the findings in a case-finding survey should be arranged.

In no sense is this written to discourage case-findings surveys but rather to call to the attention of those who would embark on such programs that there is much more to it than just preparing to examine by X-ray several thousand people in a speedy operation and then reporting that so many cases of tuberculosis were found. Rather should the plan seek the coöperation of all the agencies in the community to the end that as complete a program as possible is arranged so that the person found with tuberculosis can be properly followed up, his coöperation secured and such service as he may need provided.

In other words, while case-finding surveys may deal with large numbers, ultimately the planning must be made for the individual and, only as the problems presented in the individual patient are met, will the success of the mass survey method be attained.

BRUCE H. DOUGLAS

## AMERICAN TRUDEAU SOCIETY<sup>1</sup>

### Report of the Committee on Clinic Procedure

Dr. Herbert R. Edwards, *Chairman*

Dr. R. Alec Brown

Dr. Robert L. Mantz

Dr. Edward Kupka

Dr. Paul P. McCain

Dr. Paul S. Phelps

A meeting of the Committee was held at Gulfport, Mississippi, on October 15 through October 17, 1945, in connection with a conference of Southern State Tuberculosis Clinic Directors and Sanatoria Superintendents. As the above conference was sponsored by this Committee, it offered an unusual opportunity for our members to see at first hand some of the clinic problems pertinent to the South, and particularly in rural areas.

All members of the Committee were present, and, in addition, an invitation was extended to Dr. H. E. Hilleboe of the United States Public Health Service. Due to other pressing commitments, he was unable to attend, but assigned Dr. Weber in his place. The Committee was anxious to make available to the Public Health Service its proposed manual so that there might be as nearly as possible a unanimity of opinion on basic philosophies.

The United States Public Health Service had carefully reviewed the manual and offered a number of constructive suggestions that have been incorporated in the present draft. It is obvious, however, that, as our experience broadens in this field, there will be a need for periodic revision in the future. If possible, such revision should have the backing of the Society and the United States Public Health Service to promote as nearly a unified approach to procedure and practice in all communities as possible.

At the aforementioned meeting, the original draft of the various chapters of the proposed chest clinic manual was reviewed in detail, and a decision reached on controversial points. The Committee authorized the Chairman to arrange for the services of Mr. Basil, architect, to sketch floor plans of at least typical clinic arrangements that might be used as a basis for planning in the field. These drawings have been secured and a new chapter on clinic space has been added to the manual.

As each member of the Committee drafted different chapters of the new manual, there was need for editorial revision of the entire material to conform to a uniform style. This has been accomplished by Miss Conklin of the N. T. A. staff, in collaboration with the Chairman of the Committee.

It was the request of the Committee that, after the aforementioned revision, the manual again be submitted to members of the Committee for final approval.

<sup>1</sup> All of the committee reports published in this section were presented at the 41st annual meeting of the American Trudeau Society, Buffalo, New York, June 11, 1946.

There may be minor changes necessary following this review, but the proposed revision is essentially finished and ready for presentation to the Executive Committee.

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### Report of the Committee on Coexistent Syphilis and Tuberculosis

Dr. Hyman I. Spector, *Chairman*  
Dr. Henry D. Chadwick                      Dr. Charles R. Smith

The Committee on Coexistent Syphilis and Tuberculosis has not been active during the past two years. The Committee started off with an ambitious program which, because of the war, it was unable to carry out. As will be recalled, one of the major objectives of the Committee was to determine the effect of the arsenicals, when used in either small or large doses, on active tuberculosis. With the discovery of penicillin and its effectiveness in the treatment of syphilis, the need for the study of the effectiveness of the arsenicals on the tuberculous patient ceases. Furthermore, since reports seem to indicate that penicillin is not only generally harmless to the tuberculous patient but is even distinctly helpful to those tuberculous persons whose disease is complicated by mixed infection empyema and bronchiectasis, penicillin, therefore, becomes the drug of choice in the two coexistent diseases.

In view of the fact that a Committee on Medical Research and one on Therapy are now active with the American Trudeau Society, it is our opinion that the Committee on Coexistent Syphilis and Tuberculosis should be discontinued and its remaining unsolved problems be transferred to one of the committees mentioned above.

A few examples of the minor unsolved problems remaining are: Does a positive serological test in the course of active pulmonary tuberculosis mean coexistent syphilis? Can the toxemia of tuberculosis give a false positive reaction? Does syphilis predispose to tuberculosis? It is the belief of the Committee that these problems can be considered by either of the committees mentioned above.

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### Report of the Committee on Coöperation with the American Board of Internal Medicine

Dr. J. Burns Amberson, *Chairman*  
Dr. John B. Barnwell                      Dr. Sidney J. Shipman  
Dr. Lewis J. Moorman                      Dr. Julius L. Wilson

The Committee has continued its coöperation in an advisory capacity. This is sometimes misunderstood, and some physicians have been under the im-



pression that our Advisory Committee in the Subspecialty of Tuberculosis has authority to nominate candidates for examinations.

The proper procedure is for candidates to address their inquiries and applications to be admitted to the examinations to Dr. William A. Werrell, Assistant Secretary-Treasurer, American Board of Internal Medicine, 1 West Main Street, Madison 3, Wisconsin. After action has been taken by the American Board of Internal Medicine, the subcommittee may be consulted for advice regarding the candidate's qualifications in the field of the subspecialty.

It may be well to repeat also that candidates are not admitted to the examination in the subspecialty until they have passed the examinations in internal medicine.

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### Report of the Committee on Evaluation of Laboratory Procedures

Dr. C. Eugene Woodruff, *Chairman*

Dr. David Crombie

Dr. J. Stanley Woolley

Dr. Edgar Medlar

Mr. William Steenken

#### THE CULTURING OF SPECIMENS SUSPECTED OF CONTAINING TUBERCLE BACILLI

To-day the establishment in many communities of routine tuberculin testing of school children, high school and college students, and the mass X-raying of industrial and office workers has brought to light hundreds of cases of suspected tuberculosis. To establish the diagnosis with finality, it is necessary that the persons found by X-ray examination to have lesions should have their sputum and, in some cases, their fasting gastric content examined for tubercle bacilli. It is a known fact that a direct smear examination, in which the most suspicious sputum particles are picked, or in which a specimen has even been concentrated for smear, does not always suffice for proving or disproving the presence of tubercle bacilli. In the future, therefore, cultures of specimens should be made oftener. There are three basic requirements for the culture of a given specimen.

- 1: The specimen should be collected in a container that has been properly prepared.
- 2: Preparation of the specimen for culture must be adequate.
- 3: A proper culture medium for the isolation of tubercle bacilli must be employed.

With regard to the first requirement, it goes without saying that the sputum container (a wide-mouth glass bottle) must be completely "burned out" with sodium dichromate-sulphuric acid cleaning solution to insure the removal of any acid-fast matter that may adhere from previous use. Following this procedure the bottles must be thoroughly washed to remove any traces of the cleaning solution.

## PREPARATION OF THE SPECIMEN FOR CULTURE

To obtain adequate digestion of sputum with either dilute alkali or dilute acid, forceful agitation of the specimen is necessary. As will be mentioned later, both the addition of a detergent to sodium hydroxide and the use of Clorox have been recommended to secure digestion of the protein in sputum specimens. Such techniques are not applicable to specimens to be cultured, however, since most of the tubercle bacilli are killed by the drastic digesting agents. In using a mild digesting agent, then, the forceful agitation of the specimen becomes the key point of the procedure.

The adaptation of paint conditioning machines for use in the shaking of sputum specimens was suggested in 1942.<sup>2</sup> Originally the one gallon capacity machine was recommended, the gallon container being arranged to accommodate 10 individual sputum bottles. More recently it has been found that a shaking machine similar in type, but of one quart capacity, can be utilized. Laboratories in which such paint conditioning machines are in use for sputum preparation find them indispensable.

In some laboratories ordinary shaking machines, such as those employed in the Kahn test, are found useful for homogenizing sputum specimens. In using this type of machine it is necessary that the sputum and sodium hydroxide mixture be in a bottle sufficiently large to allow the contents to slop about. The ordinary wide-mouth 4 oz. round bottle is adequate for most specimens. It should not be filled more than two-thirds full. The rack of the shaking machine should have a cross-rod which can be clamped against the bottles.

The Committee on Evaluation of Laboratory Procedures has voted to recommend more wide-spread adoption of shaking machines for the homogenization of sputum for cultures in the belief that there will result not only a great saving in human time and effort, but also that the quality of work will be improved.

## CULTURE MEDIA

The Committee is continuing its consideration of the best possible medium for laboratory use in isolating tubercle bacilli from clinical specimens. In view of the complex nature of this problem it is deemed inadvisable to make a final report at this time. However, the Committee can recommend the following simple medium as being very effective when used in the isolation of tubercle bacilli—more effective than many of the media with complex formulae presently in wide-spread laboratory use.

*Egg-yolk-potato Medium*

## Formula

Egg-yolk.....	300 ml.
Potato-water (8 per cent glycerine).....	300 ml.

(a) The potato water is made by grating 100 g. of pared potato into 500 ml. of 8 vol. per

<sup>2</sup> W. Steenken, Jr. and M. M. Smith: J. Lab. & Clin. Med., 1942, 27, 1.

cent glycerine-water and autoclaving (in a 2-liter flask) for thirty minutes at 15 lbs. Cool to 50° C. and decant the 300 ml. necessary for the formula.

(b) Egg-yolk: Fresh hens' eggs are carefully cleaned with wet gauze, rinsed in alcohol and flamed. The egg-white and yolks are separated in the manner used in a kitchen. (As much as 20 per cent of the egg-white may be left without deleterious effect on the medium.)

(c) The 300 ml. of egg-yolk is poured into the 300 ml. of potato-water and to this is added 12 cc. of either 1 per cent laemoid solution or 1 per cent malachite green solution.\* The former dye will give a blue medium, the latter a green medium. All ingredients are thoroughly mixed, filtered through sterile gauze and tubed.

(d) In a slanted position the medium is coagulated and sterilized by a single one-hour stay in an inspissator heated to 90° C. The tubes are incubated for forty-eight hours; contaminations are rare if sterile technique is maintained throughout the procedure.

An egg-yolk-potato medium prepared as indicated above will be definitely acid in reaction, with a pH in the neighborhood of 6.5. This is important. It has frequently been taken for granted that, since the tubercle bacillus can be made to grow on either an acid or an alkaline medium, the matter of pH is immaterial. While the adaptability of *M. tuberculosis* to media varying widely in pH is well established, the fact remains that this bacillus has an optimum pH for growth just as any other microorganism has. This range is between 6.2 and 6.5. Many of the media now widely used in tuberculosis work vary in reaction from pH 7.0 to 7.4.

#### EVALUATING MEDIA FOR THE ISOLATION OF TUBERCLE BACILLI

With the increased emphasis placed on the culturing of specimens for tubercle bacilli in both sanatorium and public health laboratories, the importance of a culture medium which will afford optimum conditions for growth of the bacillus is evident. Excellent media for this purpose are available at the present time, but few people would maintain that no improvement can be made, particularly as new synthetic growth adjuvants may soon be available. However, any new medium will have to be tested against the media now in use, so it would seem an opportune time to describe the methods used in evaluating such media.

(a) *Test with stock cultures:* The first step in comparing media should be the planting of each type of medium with suspensions containing minute amounts of tubercle bacilli such as  $10^{-5}$ ,  $10^{-6}$ ,  $10^{-7}$  and  $10^{-8}$  mg. per cc. The suspensions are prepared as follows: Growth from solid or fluid medium is triturated in an agate mortar with a minimum amount of physiological salt solution until a homogeneous paste is formed. This is taken up in 10 cc. of saline and centrifuged at low speed for two minutes to remove gross clumps of organisms.

To standardize the resultant suspension an aliquot portion of suspension is removed to a weighed watch glass, evaporated over a water bath, and dried to constant weight. With allowance for the salt content, the weight of bacilli per cc. in the remainder of the suspension can then be calculated. This method is

\* The dye solution, whether laemoid or malachite green is used, should be made up in 50 per cent alcohol.

more accurate than the common practice of partially drying the organisms by pressure between layers of filter paper.

One cc. of each dilution should be used for planting 10 tubes of each medium. The tubes should be examined at weekly intervals to determine the time when growth first appears on each medium. Also record should be kept of the total colony count as well as the total number of tubes which support growth.

(b) *Tests with clinical specimens:* The above technique, carefully applied, will make possible a gross estimate of the relative merits of the media. However, since the media in question are to be used in the isolation of tubercle bacilli from clinical specimens, the test with stock cultures should be considered as merely preliminary. The crucial test of the media consists in planting them with statistically significant numbers of sputum and gastric concentrates, each clinical specimen being divided as nearly equally as possible between the two or three types of media to be tested. The tubes are examined for time of appearance and total number of colonies as indicated above.

#### SODIUM HYDROXIDE DETERGENT MIXTURES AND CLOROX

In recent years several articles have appeared on the use of detergent sodium hydroxide mixtures and Clorox to promote the digestion of sputum and body exudates before concentrating such material for the demonstration of tubercle bacilli. The addition of tergitol to sodium hydroxide does enhance the action of the latter upon the sputum or tenacious material to be digested. Clorox likewise has marked digesting properties which are even greater than the tergitol-sodium-hydroxide mixture.

In the light of our present knowledge it appears that any agent in this category, added to sodium hydroxide to increase action upon mucus or pus, must certainly intensify the action of the sodium hydroxide upon the tubercle bacillus. This effect is not so apparent in the case of sputum or exudates of high bacillary count, since organisms of atypical morphology, or ones that stain poorly, can be overlooked without any noticeable change in the total bacillary count; but in material with few bacilli it becomes very noticeable, especially in specimens where the organisms can be demonstrated only after prolonged search. The same can be said about the use of Clorox as a digesting agent.

Since the demonstration of unmistakable tubercle bacilli is the determining factor in the diagnosis of tuberculosis, it would seem best, at least for the present, to use digesting agents in weak concentrations, preferably 2 or 3 per cent sodium hydroxide, and to use a mechanical shaker to facilitate digestion. Clorox or sodium hydroxide tergitol mixtures should be used only when the materials to be examined cannot be digested by ordinary means, that is, with 2 or 3 per cent sodium hydroxide, or 3 or 4 per cent sulphuric acid, or hydrochloric acid, plus good mechanical agitation. The latter cannot be overemphasized since it minimizes drastic chemical treatment and prolonged contact of the tubercle bacilli with the digesting agent.

Specimens treated with Clorox or sodium-hydroxide-tergitol cannot be used for culture or animal inoculation because *most* of the tubercle bacilli are killed

by such treatment. It is true, however, that some of the organisms survive, and the only sure method of killing all the tubercle bacilli is by autoclaving the specimens in their containers as they are received, at 15 lbs. pressure for half an hour.

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### Report of the Medical Advisory Committee on Health Education

Dr. Charles P. Cake, *Chairman*

Dr. Kirby S. Howlett, Jr.

Dr. B. Thomas McMahon

The Medical Advisory Committee on Health Education of the American Trudeau Society has the pleasure to report that, since the beginning of the service of the present Committee, it has reviewed the manuscripts of the following proposed publications and releases of the National Tuberculosis Association:

1. The anniversary leaflet entitled *Roentgen*.
2. The pamphlet, *After the X-ray—What?*
3. The moving picture scenario, *This Is TB*.
4. The 1946 educational insert, *Just Suppose*.
5. Revision of the pamphlet, *Everybody's Doing It*.
6. Revision of the pamphlet, *Steps to Safety*.
7. The monograph on surgery in tuberculosis by Drs. Overholt and Wilson.
8. The leaflet entitled *Chest Surgery in Tuberculosis*.
9. The revision of the pamphlet, *What You Should Know about Tuberculosis*.
10. The book of biographical sketches, *The Long Adventure*.
11. The pamphlet, *Congratulations! You've Had a Chest X-ray*.
12. Audience Guide for the new Visual Aids Unit.

The Committee was also pleased to receive the endorsement by the Executive Committee of the American Trudeau Society of its policy in regard to the handling of signed manuscripts which the National Tuberculosis Association proposed to publish.

The Committee also wishes to express its pleasure in having the opportunity to serve the Health Education Department of the National Tuberculosis Association and especially wishes to thank Dr. Charles E. Lyght for the consideration which he has shown.

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### Report of the Committee on Medical Information

Dr. James C. Walsh, *Chairman*

Dr. J. Emerson Dailey

Dr. Sydney Jacobs

Dr. Cole B. Gibson

Dr. Lewis J. Moorman

Dr. John H. Skavlem

The following is a report of the Committee on Medical Information of the American Trudeau Society for the year ending June 1, 1946.

The activities of the Committee have been limited to securing articles by members of the medical profession for use in the monthly BULLETIN of the National Tuberculosis Association. Following is a list of the articles obtained for publication during the year:

*X-ray Survey Simplified*—Ezra Bridge, M.D.

*Tuberculosis in German Prison Camps*—Col. Esmond R. Long, M.D.

*Tuberculosis Search in Hospitals*—W. H. Oatway, Jr., M.D.

*Three-Way Aid to Vets*—W. H. Hickerson, M.D.

#### 1946

*Tuberculosis Problem in Louisiana*—Julius L. Wilson, M.D.

*Tuberculosis Control in British Columbia*—W. H. Hatfield, M.D.

*Tuberculosis in Industry*—B. L. Vosburgh, M.D.

*Postgraduate Education*—Maurice Campagna, M.D.

*Anti-Tuberculosis Campaign in Mexico*—I. C. Villegas, M.D.

In regard to the future, the Chairman feels that a Committee on Medical Information should be continued. Consideration might be given to extending its activities. The director of Public Relations of the National Tuberculosis Association occasionally needs assistance and advice on medical questions. This Committee could act in an advisory capacity on public relations.

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### Report of the Committee on Medical Program

Dr. Henry Stuart Willis, *Chairman*

Dr. Howard W. Bosworth

Dr. Max Pinner

Dr. H. Corwin Hinshaw

Dr. James Walsh

The Committee on Medical Program met in November of last year. The general policy, as outlined at that meeting, was to try to feature as broad a coverage as was compatible with the time allotted and men available. It was hoped that some aspects of surgery, rehabilitation, clinical problems, therapy, especially chemotherapy, could be covered and, also, that we could learn something from the war experience on air-borne infection. The further development of the program has taken place through extensive correspondence.

Since the Committee's meeting a few suggestions and comments have come in. An important one has concerned the gradual change that has taken place in the Clinical-Roentgenological Conference. As originally conceived, this conference was a very informal meeting to which men would bring their puzzles, but only those to which the final answer had been found, namely, only those in which operation, biopsy or other laboratory or postmortem examination had given answer. These cases have been submitted in some detail with case his-

ories, all of which have been submitted at the conference in mimeograph form. Since there seems to be a desire on the part of some members to revert to the old type, it is the thought of the Program Committee that this question should be discussed at the conference this year and a majority opinion expressed.

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### Report of the Membership Committee

Dr. Ernest S. Mariette, *Chairman*

Dr. Grover C. Bellinger

Dr. Alton S. Pope

The Membership Committee wishes to report that during the past year the Society has increased its membership by 309 new members, or from 2,322 to 2,631. It is expected that the membership will reach the 3,000 mark by the end of the year 1946.

One other item of interest is the election to honorary membership in the Society of Dr. Frederick G. Novy, Professor Emeritus of Bacteriology, University of Michigan.

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### Report of the Committee on Pan-American Relations

Dr. Henry C. Sweany, *Chairman*

Dr. John Alexander

Dr. Fernando D. Gomez

Dr. Jose I. Baldo

Dr. Esmond R. Long

Dr. Kendall Emerson

Dr. Hector Orrego Puelma

Dr. Max Pinner

After an indifferent beginning, the Committee on Pan-American Relations has made substantial progress. The language and transportation difficulties of former times and the uncertainties due to the war and its aftermath have been overcome or are taking on less significance. Furthermore, the material gains have been greatly augmented by the spirit of good-will already in existence.

A most significant factor in the development of desired relations has been the wholehearted coöperation on the part of the leaders of the antituberculosis work throughout Latin America, more particularly of ULAST (Unión Latino Americana de Sociedades de Tisiología). Through Dr. Fernando Gomez, Secretary of ULAST (and also a member of our Committee) the Trudeau Society has been furnished with a list of the leading Latin American thoracic specialists that "barring any involuntary error represents the most distinguished specialists of Latin America."

The Trudeau Society has created a special category designated as "Corresponding Members." The names submitted were of two classes, namely, non-

members and those already members of the Trudeau Society. To the non-members we dispatched a letter inviting the men to join, and at the same time we listed advantages and privileges of the new class of members.

To compensate partially for the high exchange rates prevalent in many of the Latin American countries, a significant reduction in cost has been made by the American Trudeau Society and the National Tuberculosis Association for the Corresponding Members. The advantages include, in addition to the special membership privileges, a reduction of the total cost to \$5.00 per year. For this fee the member will receive the AMERICAN REVIEW OF TUBERCULOSIS, the National Tuberculosis Association BULLETIN, the NEWS LETTER, and all other special features accorded regular members. Special membership certificates will be presented to each Corresponding Member.

Those already regular members of the American Trudeau Society are given the privilege of becoming Corresponding Members or, if they choose, remaining as regular members. Up to the present time, letters have gone out to 26 regular members and 80 non-members. Dr. Gomez feels assured that ultimately there will be about 150 in all who will qualify as Corresponding Members.

It is now confidently expected that the combined efforts mentioned will be productive of extensive, pleasant, beneficial and lasting intergroup relations. The soundness of this prediction has support from the interest shown and attendance at the Havana meeting of the ULAST and also the various international meetings of the last few years between our country and Mexico.

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### Report of the Committee on Postgraduate Medical Education

Dr. Paul P. McCain, *Chairman*

Dr. James D. Adamson

Dr. Victor Johnson

Dr. J. Burns Amberson

Dr. Esmond R. Long

Dr. Chesley Bush

Dr. James J. Waring

Dr. Frank A. Craig

Dr. Roy A. Wolford

There has been no meeting of the Committee during the present fiscal year.

At the request of Dr. H. E. Hilleboe, Director of Tuberculosis Control of the U. S. Public Health Service, the various members of our Committee made suggestions for the training of medical officers in tuberculosis control and also made a critical review of the courses outlined by Dr. Hilleboe. We have also kept in touch with the Committee on Medical Education and Hospitals of the American Medical Association with special reference to the placement and training of returning veterans interested in tuberculosis and diseases of the chest. The Committee was greatly disappointed to learn that, of 21,000 questionnaires sent to physicians in the Service, only 15 expressed the desire to get training in tuberculosis and only 30 in diseases of the chest. The Chairman and Dr.



Guild had a conference with Dr. Victor Johnson, Executive Secretary of the Council on Medical Education and Hospitals, last fall, and it is gratifying that Dr. Johnson has been made a member of this Committee.

On the suggestion of Dr. Kendall Emerson and Dr. John Alexander, our Committee undertook to sponsor therapeutic conferences in the northeast and the south somewhat on the plan of the Pembine Conferences held the last three years by the sanatorium physicians of Wisconsin, Minnesota and Michigan under the chairmanship of Dr. John D. Steele. On account of the shortage of staff members in most of the sanatoria, however, postponement of these conferences was deemed advisable.

The Committee would like to call attention to a most worth while post-graduate education in chest diseases for a limited number of physicians in Louisiana which is provided by the Louisiana Tuberculosis Association in coöperation with the official health agencies and the two medical schools in New Orleans. A six weeks course is provided, during which time the physicians are paid at the rate of \$300 per month. After they finish the course they will be paid \$75 per month for rendering part-time service in conducting clinics, the offices for which are to be provided and equipped by local tuberculosis associations.

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### Report of the Committee on Rehabilitation

Dr. N. Stanley Lincoln, *Chairman*

Dr. Benjamin L. Brock

Dr. Ernest S. Mariette

Dr. Charles F. Taylor

One meeting of the Committee was held at Chicago on January 23, 1946. The action taken was:

1: To recommend to the Committee on Revision of Diagnostic Standards that provision be made in the discharge classification of patients to designate said patient's need for and ability to participate in a rehabilitation program. Four specific suggestions were made.

2: To recommend to the Council of the American Trudeau Society that the Committee on Rehabilitation be made a joint one with the National Tuberculosis Association and that the membership be enlarged to include representatives of the Tuberculosis Control Division of the U. S. Public Health Service, the Veterans' Administration, and the Federal Office of Vocational Rehabilitation.

The Chairman had the honor of meeting in Washington on March 4, 5 and 6 with other workers interested in the rehabilitation of the tuberculous. This conference was called jointly by the National Tuberculosis Association, the U. S. Public Health Service, and the Office of Vocational Rehabilitation and was the most practical and productive of any attended. The edited minutes are not available as this report is submitted but the following is a preliminary statement of general conclusions:

1: The minimum hospital or sanatorium rehabilitation team should consist of a physician, an institutional nurse, a public health nurse, a medical social worker, an occupational therapist and a rehabilitation counsellor. The availability in the tuberculosis hospital or sanatorium of adequate teachers for secondary and high school subjects is assumed. The activities carried on in the hospital or sanatorium cannot usually exceed those regarded as "pre-vocational training."

2: The U. S. Public Health Service, the National Tuberculosis Association and the Federal Office of Vocational Rehabilitation will jointly provide a team to study, during the next twelve months, various rehabilitation programs in operation in continental United States. The object will be to determine (1) what is actually being done, (2) the philosophies behind these programs, and (3) the characteristics of the outstanding programs.

3: On the basis of the studies mentioned above, the National Tuberculosis Association, the U. S. Public Health Service and the Office of Vocational Rehabilitation together hope to be able to set up four rehabilitation programs in tuberculosis hospitals or sanatoria in selected sections of the country on a demonstration basis. These demonstrations, if achieved, are to be so located and manned that they will be available for study by a large group of institution and other interested personnel.

The Chairman had the honor to represent the American Trudeau Society at the annual meeting of the National Council on Rehabilitation. The central topic was the creation of rehabilitation centres for the severely handicapped. This would seem to have little if any application to the rehabilitation of the tuberculous patient at the present time.

The Chairman has not discussed with the Committee members the following subjects but believes they should be recorded in the hope that they may be helpful suggestions to future Committees.

1: The Committee has been severely handicapped by lack of specific knowledge of what rehabilitation activities were carried on in our sanatoria and hospitals. It would seem desirable that the American Trudeau Society and the National Tuberculosis Association might jointly determine a simple method to acquire these data.

2: The need of sanatorium and hospital directors is additional money and personnel to carry on rehabilitation activities. The Federal government has provided some money but this is available locally only after enabling legislation on the part of individual states. The American Trudeau Society and National Tuberculosis Association might jointly consider ways and means to promote this enabling legislation if such activities properly come within the Association's policies.

3: It appears that specific knowledge of the processes of rehabilitation is not wide-spread among physicians. Inadequate knowledge has engendered fear of a program because of the assumed high cost. Future committees might wish to undertake the preparation of a booklet of information on this subject so that thought and planning could be brought to practical action.

## Report of the Committee on Revision of Diagnostic Standards

Dr. Ralph Horton, *Chairman*

Dr. Howard W. Bosworth

Dr. Edgar Medlar

Dr. W. Edward Chamberlain

Dr. Hector Orrego Puelma

Dr. Ismael Cosio Villegas

Dr. Oscar A. Sander

Dr. Herman E. Hilleboe

Dr. John D. Steele

Dr. Paul P. McCain

Dr. George J. Wherrett

The Committee on Revision of Diagnostic Standards, after conducting preliminary work by correspondence, met in St. Louis on December 7, 1945.

It was their opinion that rather extensive revision of the 1940 edition of *Diagnostic Standards* will be necessary to include the new knowledge which has accumulated since then. This applies particularly to the following sections: pathogenesis as regards primary and reinfection phases, endobronchial tuberculosis, and pleurisy with effusion; differential diagnosis to include coccidioidomycosis, histoplasmosis and Boeck's sarcoidosis; case-finding and control to include a section on mass chest X-ray surveys; revision of the classification and descriptive summary and clinical status to be modified in order that the *Standards* may lend themselves to the use of those interpreting clinic and survey chest X-ray films; and the addition of a section on prognosis and rehabilitation.

Other parts will be in need of less extensive revision, such as that on laboratory procedures to include sputum cultures and cultures of gastric washings, and the X-ray section to include some details regarding mass X-ray surveys.

Committee members were asked to be responsible for the preliminary revision of various chapters. They were requested to collaborate in this work with their colleagues and members of other American Trudeau Society committees. As preliminary revisions of the various chapters are prepared, they are sent to the other Committee members for comment and criticism. When a complete preliminary revision is worked out, a meeting of the Committee will be held, at which time it is hoped that a tentative revision can be agreed upon. The plan is to submit this to a representative group of American Trudeau Society members whose comments and suggestions may be considered at a later meeting, following which it is hoped that a final report can be made.

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## Report of the Committee on Sanatorium Planning and Construction

Dr. Hugh B. Campbell, *Chairman*

Dr. Ralph Horton

Dr. Rollin D. Thompson

Dr. Robert E. Plunkett

Dr. Robert L. Yeager

Dr. H. McLeod Riggins

Mr. J. B. Basil, R.A.

Miss Suzanne H. Harrison, R.N.

At the meeting of the Executive Committee held on December 8 and 9, 1945,

the report of this Committee stated that a brochure had been completed and published with funds supplied by the National Tuberculosis Association.

This publication, simply and artistically assembled by an experienced hospital architect, contains illustrations showing a hospital-plot plan and floor layouts for an institution to provide accommodations for 200 patients.

Study has been given and suggestions offered for floor area requirements, relationship of units to provide efficiency and economy in operation, and other aids for architectural planning.

This part of the Committee's assignment is completed.

Though no Committee meetings have been held in the past several months, the second part of the program is progressing. The old manual on sanatorium construction published in 1939 is now being revised. When complete, the revision will be much more comprehensive than the volume it supplants.

Mr. Basil is analyzing the various units and subdivisions shown in the drawings referred to in the first part of this report. This analysis is being done in some detail, both in relation to departments and to the units which they contain.

The Committee, through the mail, receives his memoranda for comment and criticism. Some months must elapse before all the facts can be properly assembled and correlated. For this purpose, it is hoped to have a meeting of the Committee either in the late summer or early fall.

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### Report of the Committee on Therapy

Dr. H. Corwin Hinshaw, *Chairman*

Dr. John B. Barnwell

Dr. Kirby S. Howlett

Dr. Robert G. Ferguson

Dr. John D. Steele

Dr. John N. Hayes

Dr. Henry C. Sweany

The Committee on Therapy assembled on but one occasion during the past fiscal year. The meeting was held in Rochester, Minnesota, on January 11 and 12, 1946, for the purpose of reviewing the available information concerning streptomycin in the treatment of experimental and clinical tuberculosis. Dr. Kirby Howlett was designated as chairman of the subcommittee constituted to prepare a report summarizing the material presented. This report is as follows:

#### STREPTOMYCIN FOR TUBERCULOSIS

Evidence of the striking ability of streptomycin to suppress and at times to eradicate experimental tuberculosis in guinea pigs is already well known from published data. The marked discrepancy which may be expected to exist between results in experimental animals and results in human patients is equally well known from previous experiences with other chemotherapeutic agents. To permit even a preliminary and tentative estimate of the potential value of streptomycin in the treatment of tuberculosis in patients, therefore, a highly critical

review of available cases already treated with the drug was obviously necessary.

At a meeting held in Rochester, Minnesota, on January 11 and 12, 1946, an opportunity was given the Committee to make such a review of all patients with tuberculosis treated with streptomycin up to that time by the Mayo Clinic group. The series reviewed consisted principally of several patients in each of the following classifications:

- 1: Tuberculosis of the genito-urinary tract; a series of cases with tuberculosis of the remaining kidney and other genito-urinary organs, who had at some previous date already had a nephrectomy.
- 2: Tuberculous adenitis and tuberculous sinuses of long standing, resistant to ordinary therapeutic attack.
- 3: Tuberculosis of the skin.
- 4: Generalized miliary tuberculosis with meningitis.
- 5: Hematogenous and acute exudative pulmonary tuberculosis.
- 6: Chronic pulmonary tuberculosis with recent acute bronchogenic spreads of disease.
- 7: A small miscellaneous group (tuberculous pharyngitis, laryngitis and endobronchial tuberculosis).

A total of 63 cases were reviewed.

In the light of the observed course of disease in these treated tuberculosis cases and in view of the reported experience with streptomycin in the treatment of other disease, the following tentative conclusions were reached:

(1) Streptomycin has the requisite qualities for clinical use. Local and systemic toxic effects have been relatively mild and may be due to impurities. Preliminary tests made with a small amount of chemically pure streptomycin suggest that the drug itself is actually devoid of immediate local or systemic toxicity. Much more extensive study of toxicity is needed, however, especially to better determine whether toxicity may result from long-term use of the drug in a chronic disease. The Committee is informed that such toxicity studies are now under way.

(2) Preliminary laboratory and clinical investigations suggest that streptomycin may extend the range of chemotherapy to several types of infection with organisms resistant to penicillin and other agents. Since there is need for further clinical investigation in several fields, only a fraction of the total small supply of the drug is available for tuberculosis.

(3) In the small series of several types of clinical tuberculosis reviewed, in no instance was streptomycin rapidly curative in the manner so commonly observed in susceptible acute infections—pneumococcus pneumonia, for example—treated with penicillin. In no case was an established tuberculous infection completely eradicated. This limitation may eventually be accounted for by the inherent qualities of tuberculous disease, rather than by intrinsic deficiencies in the chemotherapeutic agent. It indicates to the Committee, however, the great desirability of continuing laboratory research in the quest for an agent more effective against tuberculosis.

(4) In the dosage and treatment schedules employed, streptomycin demonstrated only a questionable or limited effectiveness against chronic phases of pulmonary tuberculosis. Moreover, in several types of extrapulmonary tubercu-

losis a tendency was observed for lesions to relapse or for tubercle bacilli to reappear after treatment was stopped, even among patients whose response to streptomycin was favorable during treatment.

(5) While the limitations of streptomycin on the basis of present evidence are thus apparent, the cumulative evidence from the patients reviewed suggests strongly that streptomycin is capable of influencing the course of certain types of tuberculous disease in a favorable manner and of exerting a suppressive effect upon previously progressive tuberculosis. While the favorable influence observed varied markedly in degree in different patients, improvement of some degree in patients under treatment was remarkably consistent throughout the series. In several instances the rate of improvement was unusually rapid for tuberculosis. These facts, plus the ability of the drug to stem the tide and even to reverse the trend in a number of patients with disease previously shown to be progressive, and of types and behavior generally recognized as carrying the most unfavorable prognosis, make it unlikely that the results observed can all be attributed merely to natural processes of healing.

(6) A number of patients showed a rate of improvement not strikingly faster than is often observed in similar cases with good resistance on an ordinary regimen. In no case was a direct bactericidal effect demonstrated. This fact and the limitations indicated in items 3 and 4 above suggest that streptomycin, when effective, may act purely in a suppressive rôle against the tuberculous infection and as a deterrent to further progression of disease. The exact mechanisms involved, however, have not yet been demonstrated.

(7) Experience with streptomycin to date is grossly inadequate yet to establish optimum dosage, length of treatment and schedules of treatment. Pertinent to these considerations is the demonstration by Dr. Guy Youmans of Northwestern University that formerly drug sensitive tubercle bacilli have the quality of developing a resistance to streptomycin, often of high degree, when these organisms are tested *in vitro* following extensive treatment of the patient with the drug.

The conclusions enumerated indicate the vast uncertainties which now exist regarding the place of streptomycin in tuberculosis therapy. The preliminary and tentative nature of the conclusions presented by the Committee must be repeatedly and strongly emphasized. The Committee is fully aware of the danger that errors in clinical judgment may lead us astray in judging the therapeutic effects of any specific measure in a disease whose behavior is as unpredictable as that of tuberculosis. The danger of basing such judgment on a relatively small series of patients is apparent to anyone experienced in the field. Hence much more study and observation will be required before streptomycin can gain recognition as an agent of established value against tuberculosis. The Committee believes, however, that preliminary observations are sufficiently encouraging to justify further projects in clinical investigation of the drug when supplies permit. Such projects are, indeed, necessary not only to define the possibilities and limitations of streptomycin therapy, but also to determine many further details influencing optimum therapeutic effect.

Our Committee is reliably informed that present plans for the allocation of

streptomycin are approximately these: All manufacturers are pooling their streptomycin output. This is being diverted to (a) various federal services including the Army, the Navy, the Veterans' Administration and the U. S. Public Health Service, and (b) civilian investigators. All civilian supplies are being allocated through the Committee on Chemotherapeutics and Other Agents of the National Research Council under the chairmanship of Dr. Chester Keefer, 65 East Newton Street, Boston 18, Massachusetts. The plan of this Committee, as now stated, is to use the limited supplies of streptomycin largely for investigation in certain specified nontuberculous infections. The following statement has been made by Dr. Keefer's committee regarding tuberculosis:

"For the present only those cases which are now under treatment will be studied. A broader program for the study of tuberculosis is planned, but it cannot be expanded at the present time due to inadequate supplies of streptomycin. It is the hope of the Committee on Chemotherapeutics and Other Agents to explore this problem with the Subcommittee on Tuberculosis of the National Research Council and the Research and Chemotherapy Committee of the National Tuberculosis Association. The medical profession will be kept informed of the developments."

The Committee on Therapy of the A. T. S. has not yet been informed of the extent to which it will be consulted in the development of plans for further clinical investigation in tuberculosis. It is apparent, however, that the supply of streptomycin available for tuberculosis will be, at best, extremely small for many months to come. The cost of the drug is, at present, high. Hence, though based on admittedly inadequate evidence, the following suggestions are offered in the hope that they may lead to the most efficient and productive use of the small supplies when these become available.

(1) Present evidence indicates that streptomycin may best be regarded as a potentially useful adjunct to approved and time-tested therapeutic procedures in tuberculosis, but by no means as a substitute for them. Hence, under no condition should either rest-therapy, an indicated collapse therapeutic procedure, or such established measures as nephrectomy and spine fixation be postponed or rejected with the thought that streptomycin will eventually become available and make such treatment unnecessary.

(2) In the uniformly fatal forms of tuberculosis, generalized miliary tuberculosis and tuberculous meningitis, the ability of streptomycin to accomplish such phenomena as clearing of lesions according to X-ray observations, resolution and encapsulation of pulmonary foci histologically, elimination of bacilli from spinal fluid, etc., has constituted a strong link in the chain of evidence for a specific suppressive action of the drug. In the several such patients reported to the Committee, however, none has actually made a clinical recovery. It is highly doubtful, therefore, whether use of the large quantities of drug necessary to hold such infections temporarily in check is justifiable until streptomycin is more freely available.

(3) Since present evidence suggests only questionable and limited influence upon the chronic phases of pulmonary tuberculosis, the drug should obviously not be diverted in this early period of investigation to patients who are doing

reasonably well on other types of therapy. Though certain types of chronic extrapulmonary disease appear to be favorably influenced by streptomycin, many such patients will not have their chances for recovery seriously impaired by a few months' delay. Treatment of such patients with streptomycin may, therefore, better be deferred until supplies are more adequate.

(4) In the light of present evidence, the value of streptomycin as a potentially life saving measure seems most likely to be demonstrated in patients with pulmonary tuberculosis who have serious acute spreads of disease while under treatment. Also patients with acute ulcerating lesions of the tracheobronchial tree and larynx and extensions of tuberculosis which sometimes follow pulmonary resection should constitute excellent subjects for streptomycin treatment. Such patients should, we think, receive priority in the allocation of streptomycin so long as the supply of the drug restricts treatment to only a few cases. Preferential selection for treatment is even more clearly in order if the acute spread be to a contralateral lung during or following either an irreversible collapse procedure or pulmonary resection.

(5) To expedite more accurate determinations of the place of streptomycin in tuberculosis therapy, and to avoid the harm which can result from erroneous or premature judgment, the Committee considers it imperative that further investigation be carried on by tuberculosis clinicians thoroughly familiar by experience with the clinical course of this disease in all its variable aspects. It is our strong recommendation, therefore, that supplies of streptomycin designated for tuberculosis be allocated first to such men, with preference to those attached to tuberculosis sanatoria and hospitals well equipped to facilitate accurate evaluation studies.

The Committee on Therapy obviously has no control of publicity on streptomycin appearing in the lay press. It can only point out the serious harm that can result from such premature publicity by uninformed or incompletely informed writers, even when based on data from authorized investigators. The harmful effects of such publicity should be clear from previous experience with promin, promizole, diasone, etc. Editors can avoid a real disservice to both patients and public if such publicity is withheld until release is approved by responsible investigators and committees.

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### Report of the Committee on Tuberculosis among Hospital Personnel

Dr. Leopold Brahdy, *Chairman*

Dr. Howard W. Bosworth

Dr. William H. Oatway, Jr.

Dr. Gordon M. Meade

Dr. Berthold S. Pollak

Dr. Robin C. Buerki

Mr. F. Stanley Howe

Mr. Moir P. Tanner

#### PART I

The accumulated evidence on occupational tuberculosis among employees in general hospitals makes it imperative that hospitals take effective action to



control the spread of this disease within their own institutions. In many states the Workmen's Compensation Laws make the employing hospitals liable for medical costs and disability payments to their own employees who have the misfortune to acquire tuberculosis because of their work. This misfortune to the individual and the financial burden on hospitals are unnecessary because most occupational tuberculosis is preventable, and the rest can be mitigated by discovery in the earliest stages.

Not only may nurses and other personnel acquire the disease from patients who were admitted for some completely unrelated disease, but patients, especially children, may be infected by the personnel.

The discovery of early pulmonary tuberculosis by X-ray examinations of groups of apparently healthy people has become part of public health functions everywhere. Such mass surveys are the main weapons in the war to eliminate tuberculosis. Industry, schools, clubs, neighborhoods and whole towns have organized for X-ray case-finding. An ideal place and group for such a survey is in hospitals among the patients admitted for any reason. In addition to the necessity for protecting their own employees and their own patients, hospitals should institute case-finding among all admissions because this field of public health is properly a function of hospitals. It is an essential health service which a hospital can render its community better than any other agency. The hospital should take its rightful place in public health activities and should have financial support from public health funds in this field.

Tuberculosis sanatoria have special standards for the health supervision of their personnel. This Committee recommends that all other institutions for the care of the sick now adopt a Minimum Standard of Tuberculosis Control.

1: All patients shall have an X-ray film of the lungs on admission. For children, tuberculin testing may be used, and the negative reactors need not have chest X-ray films.

2: All employees shall have an X-ray of the chest on beginning employment and annually for four years.

3: Among student nurses the X-ray examination is to be more frequent and all students should be tuberculin-tested on enrollment and annually thereafter.

This is a *minimum* standard for immediate adoption. After such control is functioning efficiently, case-finding among employees should be intensified by lengthening the time that annual X-ray films are required, by more frequent X-ray examinations, by wider use of and more frequent tuberculin testing.

Patients found to have communicable tuberculosis must be isolated. The tested techniques for prevention of infection of others must be taught to the patient and to all personnel in attendance. No opportunity should be missed to enlighten the patient on the benefit that he has received by the early discovery of a disease for which he did not seek diagnosis.

## PART II

Control of tuberculosis in hospitals has been under discussion by the American Hospital Association for some time. The U. S. Public Health Service has had plans in this field ready for action with the advent of peace. The American

Trudeau Society has investigated this problem and published reports for several years.

In 1945 the Joint Committee of members of the American Trudeau Society and members of the American Hospital Association was appointed with the main objective of promoting coöperation among interested groups so that the plans of each one may be realized in actual accomplishment.

In September, 1946 the U. S. Public Health Service and the American Hospital Association will initiate an active campaign to have all hospitals make case-finding among personnel and admissions a part of the regular hospital routine. This will mark the first step in large scale accomplishment of the Committee's objective. The American Hospital Association in coöperation with the National Tuberculosis Association and the U. S. Public Health Service has developed a "kit" containing information on how to conduct mass radiography in hospitals. This kit consists of leaflets of educational literature for administrators and for the public. Other leaflets give instructions on the various problems confronting hospitals in doing this work. The American Hospital Association will distribute this kit among its members and perhaps to other hospitals that need the help to be derived from this collection of pamphlets. The U. S. Public Health Service will distribute this kit among health officers and roentgenologists. The National Tuberculosis Association will distribute it to its state and local associations.

The Committee believes that the distribution of this "kit" with accompanying letters will produce major results in the campaign to have all hospitals do tuberculosis case-finding on personnel and admissions.

The Committee calls the attention of the Society to other important developments which will aid in achieving the objectives of complete tuberculosis control in hospitals.

*Hospitals*, a journal for administrators, will devote one issue entirely to tuberculosis in hospitals (probably the July or August number). Besides the questions under consideration by this Committee, the number will cover other tuberculosis problems facing hospital administrators.

The U. S. Public Health Service has allocated funds to the States for tuberculosis control. Part of these funds will be available for long-term demonstrations of case-finding within large hospitals.

The U. S. Public Health Service has produced an exhibit and a motion picture on case-finding within hospitals. Both of these will be shown in all parts of the country.

The Joint Committee strongly recommends the wide distribution of this "kit," of the June issue of *Hospitals* and of the U. S. Public Health Service motion picture and exhibit.

The Joint Committee commends the educational and financial aid program of the U. S. Public Health Service to encourage hospital participation in tuberculosis control.

This Committee calls for continuation of the individual and coöperative activities of the American Hospital Association, of the U. S. Public Health Service, of the American Trudeau Society and of the National Tuberculosis

Association. It suggests that more local chapters of the National Tuberculosis Association participate financially or otherwise in assisting hospitals with the routine case-finding programs.

There are other health organizations which should take their place in this health endeavor, such as the American Medical Association, the American College of Surgeons, the American Public Health Association and the National Nursing Council. This Committee recommends that the National Tuberculosis Association request interested associations and their local chapters (1) to consider and to endorse the programs of the American Hospital Association and of the U. S. Public Health Service; (2) to develop their own educational programs on hospital case-finding for those responsible for hospital procedures and also for the public; and (3) to find other effective ways to assist in making tuberculosis case-finding part of the routine of all hospitals as soon as possible.

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### Report of the Committee on Tuberculosis in Industry

Dr. Leroy U. Gardner, *Chairman*

Dr. Lloyd Hamlin

Dr. Oscar A. Sander

Dr. T. Lyle Hazlett

Mr. B. E. Kuechle

Dr. Herman E. Hilleboe

Mr. C. D. Selby

Dr. Ada Chree Reid

Mr. William A. Doppler, *Secretary*

The Committee on Tuberculosis in Industry reports that it held a meeting on November 13, 1945, at the Schenley Hotel in Pittsburgh, Pennsylvania. There were present: Drs. Gardner, Hamlin, Reid, Sander, Kiefer representing Dr. Hilleboe, Messrs. Kuechle and Doppler. Drs. Shepard, Selby and Hazlett, the other members of the Committee, were unable to attend the meeting. Present also, by special invitation, were: Colonel John N. Andrews, Officer in Charge of Postwar Planning, Selective Service System, Washington, D. C.; Dr. Harvey Bartle, Chairman, Committee on Standardization of Industrial Medical Examinations, American Medical Association, Chicago, Illinois; Dr. A. J. Lanza, Associate Director, Welfare Department, Metropolitan Life Insurance Company, New York, New York; Richard Lutz, Personnel Director, Falk Corporation, Milwaukee, Wisconsin. The National Tuberculosis Association staff was represented by Mrs. Julie E. Miale, R. N. and Mr. Holland Hudson.

In addition to the annual meeting the Committee has been operating by mail throughout the whole year.

#### 1. TUBERCULOSIS AND INDUSTRIAL EMPLOYMENT

The main topic of discussion at the annual meeting was the manuscript on *Tuberculosis and Industrial Employment* prepared for the Committee by Dr. Oscar A. Sander. The manuscript was read completely and discussed sentence

by sentence and at times, word for word, until entire agreement on all points was reached.

Upon motion, it was voted to ask the Executive Committee of the American Trudeau Society to advise the National Tuberculosis Association to publish the monograph in its present revised form and to give this code of fair employment standards extensive field trial. It was also suggested that after publication it be made available to all members of the American Trudeau Society.

Meanwhile, the Executive Committee has read the manuscript and offered suggestions which were carefully considered by the author and your Chairman. Mr. Doppler reports that the manuscript is now at the printer.

## 2. TUBERCULOSIS, INDUSTRIAL NURSING AND MASS RADIOGRAPHY

The Industrial Service of the National Tuberculosis Association asked the members of our Committee to read a manuscript entitled *Tuberculosis, Industrial Nursing and Mass Radiography* prepared by Mrs. Julie E. Miale, R. N. and sponsored by a committee of the National Organization of Public Health Nursing. We have been told by the author that this Committee's suggestions and advice have been most helpful.

The manual was completed in January, 1946, and 5,000 copies have been distributed since that date. A second edition is now in preparation.

## 3. INDUSTRY, TUBERCULOSIS, SILICOSIS AND COMPENSATION—A SYMPOSIUM

Twelve authors have contributed to this symposium:

Wm. P. Shepard—*Tuberculosis and War Industry*

Herman E. Hilleboe and David M. Gould—*Conquest of Tuberculosis in Industry*

C. D. Selby—*The Attitude of Industry toward X-ray Examinations of the Chest*

Ada Chree Reid—*Control of Tuberculosis in an Industrial Group*

L. E. Hamlin—*Review of Silicosis for the Industrial Hygienist and Medical Practitioner*

Oscar A. Sander—*The Respiratory Hazards of Electric Arc Welding*

Leroy U. Gardner—*Elements of Diagnosis and Prognosis in Pneumoconiosis*

P. J. Bamberger—*Management of the Silicotic Patient*

A. J. Lanza—*Aluminum Therapy in the Prevention and Treatment of Silicosis*

George W. Wright—*Medical Aspects of Compensation for Partial Disability from Silicosis*

Leopold Brahdý—*Occupational Diseases—The Physician and the Law*

B. E. Kuechle—*Occupational Disease Liabilities—Financial and Humanitarian*

Due to unforeseen difficulties in delivery of paper stock and tie-up in the bindery, the publication originally scheduled for distribution January 15, 1946, will not be available before the end of May.

The Committee has had occasion to be of help to National Tuberculosis Association services on several problems by expressing opinions and giving counsel. These problems included follow-up procedures, reports to industrial physicians of X-ray survey findings, pamphlets in preparation and so forth.

In concluding this report, the Committee wishes to point out that tuberculosis control in industry is only part of the larger picture of industrial health and that, whenever possible and practical, assistance should be given to bring general health services to plants, particularly the small ones which cannot afford full- or part-time physicians and nurses.

It is thought desirable that tuberculosis associations exercise leadership in this field because experience has shown that interest aroused by chest surveys usually leads to requests for more extended health services.

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### Report of the Committee on Tuberculosis in Mental Hospitals

Dr. Robert E. Plunkett, *Chairman*

Dr. Harold S. Hatch

Dr. Cedric Northrup

Dr. Edward Kupka

Dr. Maxim Pollak

#### PREAMBLE

Available information indicates that tuberculosis among patients in mental hospitals presents a problem of serious proportions from the standpoint of morbidity, mortality, public health and economics. The problem reaches far beyond the walls of the institution and directly affects the family and community of each employee and patient.

In order that the size of this problem may be accurately defined and that appropriate action may be taken for its solution, it is recommended that each state:

- 1: Establish a service, preferably within the framework of existing agencies or departments, together with the assignment of competent staffs, to direct a program for the control of tuberculosis in mental hygiene institutions on a state-wide basis. Because of the communicable nature of the disease and the likelihood of spread outside of the institution, the state health department should assume an important place in the promotion, organization, and possibly in the administration of the control program.
- 2: Obtain a current appraisal of the prevalence of tuberculosis in each institution by:

- (a) X-raying all patients
- (b) X-raying all employees

- 3: Provide for the segregation of all active or probably active tuberculosis patients as soon as possible. In more populous states, consideration might be given to the concentration of tuberculosis patients in one or more institutions, depending on the size and geographical distribution of the problem.

- 4: Establish in the institutions caring for the tuberculous a medical and nursing service commensurate with modern public health and medical practice. Utilize the medical and nursing staffs of the special tuberculosis centres, whenever such exist, as consultants or administrators of the entire tuberculosis control program.

- 5: Provide for the X-raying of all patients on admission and for preemployment X-raying of all applicants for work.

- 6: Re-X-ray periodically all patients and all employees.

7: In order to provide for the necessary follow-up examinations of families of patients as well as of patients on parole or discharged from mental hospitals, complete case reporting to the appropriate health department should be established and maintained.

#### DETAILED REPORT

Available information indicates that tuberculosis among patients in mental hygiene hospitals presents a problem of serious proportions from the standpoint of mortality, morbidity, public health and economics.

*Tuberculosis mortality:* In New York State, in 1940, the average death rate from tuberculosis in institutions for mental diseases and mental defects was approximately twelve times that of the population as a whole. The annual average death rate in these institutions for the three years 1937-1939 ranged from approximately 100 per 100,000 in one institution to 1,500 per 100,000 in another. The annual average tuberculosis death rate in all the institutions during these three years was 618 per 100,000 as compared with 51 per 100,000 for New York State as a whole. Comparable mortality rates prevail in other states. For example, the death rate per 100,000 among inmates of mental hygiene institutions in Massachusetts for 1943 was 529, Michigan 460, Wisconsin 357, and Minnesota 789. Information from the State of Washington gives a rate of 1,027.

*Number of persons in mental hygiene hospitals:* The population in mental hygiene hospitals in the United States in 1942, according to the 1945 report of the Bureau of Census, was 497,938. Eighty-seven per cent of the patients are cared for in state-owned hospitals, and the balance are distributed among veterans' or county and city hospitals, as well as private institutions. (See table 1 at end of this report.)

It is interesting to note that according to the same report the hospitalization rates in state mental hospitals, although averaging 330.5 patients hospitalized per 100,000 population, show a wide range from a low of 64.4 in Wisconsin to a high of 589.3 in New York. The State of Washington reports a hospitalization rate of 916.4. These figures do not necessarily represent a difference in the prevalence of mental disease in the various states, but rather serve as a numerical index of facilities maintained by the states and do not include patients cared for in county, city or other institutions.

*Number of mental defectives:* The total population of the institutions for mental defectives and epileptics at the end of 1942 was 114,864. This does not represent the total number of mental defectives and epileptics, inasmuch as in some states these patients are cared for in hospitals for mental diseases. (See table 2 at end of this report.)

*Estimated morbidity:* Information from many sources indicates that the prevalence of tuberculosis among the mentally ill is many times that in the general population. The experience of the New York State Department of Health is presented as being fairly representative of the problem throughout the country. More than four years ago, this Department, in conjunction with the State

Department of Mental Hygiene, inaugurated a program of tuberculosis control in 26 state institutions for patients with mental diseases, mental defectives and epileptics. The initial step in this program was the X-raying of all patients and employees of these institutions. Two 4x5" photofluorographic units have been used, all questionable cases being re-X-rayed on 14x17" celluloid films. A total of 73,658 patients in hospitals for patients with mental disease were X-rayed, among whom 4,133, or 5.6 per cent, were diagnosed as having active or probably active pulmonary tuberculosis. An additional 3,964, or 5.4 per cent, showed X-ray evidence of apparently healed pulmonary tuberculosis.

In the schools for mental defectives, including the colony for epileptics, 15,400 patients were X-rayed, of whom 377, or 2.4 per cent, had active or probably active tuberculosis and 268, or 1.7 per cent, had apparently healed tuberculosis.

A total of 17,447 employees of these institutions were X-rayed, of whom 180, or 1.0 per cent, were found with active or probably active tuberculosis, and 473, or 2.7 per cent, were found with apparently healed tuberculosis.

Other investigators have reported results similar to those obtained in New York State. It seems reasonable to estimate that, on the basis of the prevalence rate of 5.6 per cent among patients in public mental hospitals, at the end of 1942 there were 24,223 cases of active or probably active pulmonary tuberculosis among the patients in public mental hospitals throughout the country, and an additional 5.4 per cent, or 23,358 patients, with apparently healed tuberculosis. Among patients in institutions for mental defectives and epileptics, the number of cases of active or probably active tuberculosis may be estimated at 2,757, and the number with apparently healed lesions at 1,953. Thus, there probably is a total of more than 27,000 cases of active or probably active tuberculosis in all hospitals, and an additional 25,000 cases of apparently healed tuberculosis.

#### THE EXTENT OF HAZARD

The importance of the disease is, however, not limited to the patients themselves. The high prevalence of the disease among the patients presents a hazard to the health of the employees in these institutions. The results of the survey in New York State showed a definite correlation between the prevalence of active or probably active tuberculosis among the patients and that among employees, since, in general, more tuberculosis was found among employees in institutions where the prevalence among patients was higher than among employees in institutions where the prevalence of the disease was low.

The presence of tuberculosis among employees also creates a community health problem. The family, household members and other intimate contacts are exposed to the risk of infection and possibly of disease. Consequently, the chain of infection is extended beyond the environment of the institutions.

Those patients whose mental condition has improved sufficiently to permit their parole or discharge to their homes, even though their pulmonary lesions are not completely arrested, are potential sources of infection to their families and other contacts in the communities to which they return.

## ECONOMIC ASPECTS

It is generally recognized that poverty and tuberculosis are frequently associated. The economic burden, as a result of the development of tuberculosis in a member of the family, is beyond the ability of all but a very small percentage of families to carry. Therefore, the economic burden to families of mental patients who may be paroled or discharged to their homes, cannot be ignored in appraising the significance of this problem.

Furthermore, in those states where tuberculosis among employees has been declared compensable, the financial aspect increases the importance of tuberculosis in these institutions. In New York State, for example, for the first five years after tuberculosis was declared compensable, the total cost of compensation for this disease among 144 employees of state mental institutions was over \$1,304,000. The effect of the tuberculosis control program, including the pre-employment X-ray examination of all prospective employees, is shown by the decrease in the number of compensation claims paid because of the development of tuberculosis, in the following table:

*Department of Mental Hygiene  
Tuberculosis cases awarded compensation*

<i>Period</i>	<i>Number of cases</i>
7/1/35 to 6/30/36.....	5
7/1/36 to 6/30/37.....	22
7/1/37 to 6/30/38.....	30
7/1/38 to 6/30/39.....	41
7/1/39 to 6/30/40.....	46
7/1/40 to 6/30/41.....	49
7/1/41 to 6/30/42.....	75
7/1/42 to 3/31/43.....	31
4/1/43 to 3/31/44.....	27
4/1/44 to 3/31/45.....	12

## SUGGESTED CONTROL PROGRAM

The establishment, without delay, of a service in each state in which such a service is not now available, should provide for:

## 1: The chest X-raying of:

- (a) All patients in mental hygiene hospitals and institutions for mental defectives or epileptics.
- (b) New admissions to these institutions.
- (c) Patients before discharge or parole from these institutions.
- (d) All employees of these institutions.
- (e) Applicants for employment and the elimination of all applicants showing evidence of presumably active tuberculosis.

## 2: The segregation of all patients with active or possibly active tuberculosis. If the size of the problem is sufficiently large, the establishment of one or more tuberculosis centres at existing mental institutions. This may require the construction of new buildings or the adaptation by renovation or remodeling of existing buildings.



- 3: The institution of a communicable disease technique in the tuberculosis wards by physicians, nurses and attendants.
- 4: Clinical appraisal and therapy for tuberculosis patients.
- 5: Annual X-ray reexamination of all patients in all institutions, at least until more knowledge becomes available regarding the rate of development of tuberculosis in the various groups of patients.
- 6: X-ray reexamination every six months of all employees and every three months of employees on tuberculosis wards or services.
- 7: The follow-up examinations of paroled or discharged patients and their contacts by local health departments.
- 8: Establishment of a system of records which will provide necessary clinical, epidemiological and statistical data.

The service should include complete bacteriological, clinical and pathological laboratory facilities; adequate X-ray equipment; and clinical and statistical and clerical personnel necessary for modern medical and surgical practice and research. In other words, the service should, with minor exceptions, aim to meet the standards of tuberculosis hospitals as prescribed by the American Trudeau Society.

The medical personnel engaged to carry on these services should have special training in tuberculosis and other diseases of the lungs. When qualified specialists are not available, training opportunities for such should be provided. In addition to being responsible for the study and treatment of patients in the tuberculosis centres, these physicians should participate in the periodic resurveys of patients and employees in the institutions not designated as tuberculosis centres. Moreover, they should act as consultants in problems associated with all pulmonary diseases and other forms of tuberculosis.

In order to provide a satisfactory and safe nursing service, it would be necessary to employ nurses, at least for the key positions, who possess the appropriate educational and experience qualifications.

#### ORGANIZATION

In planning its administrative program, each state should make a careful appraisal of existing facilities dealing with tuberculosis control. Whenever feasible, the available facilities of the state departments of health, state or local tuberculosis hospitals, state or local tuberculosis clinics, other official agencies engaged in tuberculosis control, or state or local tuberculosis associations should be used either directly as participants in the program, or as consultants.

Regardless of what may be the administrative organization, it is essential, particularly in states in which the problem is relatively large, to have a physician employed in the appropriate department and on a state-wide level to be designated as director of tuberculosis services or some similar title.

TABLE 1

*Resident patients at end of the year 1942 in hospitals for permanent care of psychiatric patients, and estimated number of cases of pulmonary tuberculosis\* in State Hospitals, in the United States, geographic divisions, and in each State*

DIVISIONS AND STATES	RESIDENT PATIENTS AT END OF YEAR					RATE** (STATE HOSPITALS)	ESTIMATED CASES OF PULMONARY TUBER- CULOSIS IN STATE HOSPITALS*	
	Total	State Hospitals	Veterans' Hospitals	County and City Hospitals	Private Hospitals		Clinically Significant (5.6 per cent)	Apparent- ly Healed (5.4 per cent)
United States.....	497,938	432,550	32,348	21,256	11,784	330.5	24,223	23,358
New England.....	43,414	39,298	2,231	—	1,885	469.0	2,201	2,122
Maine.....	2,624	2,613	—	—	11	318.8	146	141
New Hampshire.....	2,305	2,301	—	—	4	484.8	129	124
Vermont.....	1,798	1,052	—	—	746	308.8	59	57
Massachusetts.....	25,746	23,106	2,231	—	409	543.0	1,294	1,248
Rhode Island.....	2,900	2,750	—	—	150	382.9	154	149
Connecticut.....	8,041	7,476	—	—	565	422.3	419	404
Middle Atlantic.....	136,492	120,629	6,408	5,977	3,478	450.2	6,755	6,514
New York.....	80,616	75,913	3,329	—	1,374	589.3	4,251	4,099
New Jersey.....	18,924	11,052	1,568	5,977	327	262.1	619	597
Pennsylvania.....	36,952	33,664	1,511	—	1,777	347.1	1,885	1,818
East North Central....	98,478	79,620	7,829	9,193	1,836	295.3	4,459	4,299
Ohio.....	21,853	19,750	1,549	305	249	284.9	1,106	1,067
Indiana.....	10,643	9,111	1,512	—	20	262.2	510	492
Illinois.....	35,008	31,311	3,255	—	442	394.8	1,753	1,691
Michigan.....	19,379	17,440	1,213	—	726	316.7	977	942
Wisconsin.....	11,595	2,008	300	8,888	399	64.4	112	108
West North Central...	46,617	38,882	2,369	4,460	906	300.8	2,177	2,100
Minnesota.....	11,677	10,537	1,086	—	54	396.4	590	569
Iowa.....	9,128	6,537	1,283	1,027	281	269.5	366	353
Missouri.....	12,696	8,843	—	3,433	420	238.0	495	478
North Dakota.....	2,008	2,008	—	—	—	343.5	112	108
South Dakota.....	1,591	1,591	—	—	—	272.5	89	86
Nebraska.....	4,409	4,339	—	—	70	350.7	243	234
Kansas.....	5,108	5,027	—	—	81	291.9	282	271
South Atlantic.....	58,792	53,811	3,465	38	1,478	298.2	3,013	2,906
Delaware.....	1,204	1,204	—	—	—	437.1	67	65
Maryland.....	9,503	7,102	1,341	38	1,022	370.6	398	384
Dist. of Columbia...	6,562	6,562	—	—	—	793.9	367	354
Virginia.....	10,718	9,524	1,108	—	86	340.5	533	514
West Virginia.....	3,928	3,928	—	—	—	213.4	220	212
North Carolina.....	7,682	7,508	—	—	174	216.9	420	405
South Carolina.....	4,757	4,735	—	—	22	250.6	265	256
Georgia.....	9,268	8,112	1,016	—	140	265.0	454	438
Florida.....	5,170	5,136	—	—	34	260.0	288	277

TABLE 1—*Concluded*

DIVISIONS AND STATES	RESIDENT PATIENTS AT END OF YEAR					RATE** (STATE HOSPITALS)	ESTIMATED CASES OF PULMONARY TUBERCULOSIS IN STATE HOSPITALS*	
	Total	State Hospitals	Veterans' Hospitals	County and City Hospitals	Private Hospitals		Clinically Significant (5.6 per cent)	Apparently Healed (5.4 per cent)
East South Central....	26,211	22,434	2,571	1,010	196	210.8	1,256	1,211
Kentucky.....	7,050	6,469	495	—	86	236.8	362	349
Tennessee.....	6,841	5,776	—	1,010	55	198.1	323	312
Alabama.....	7,210	5,833	1,345	—	32	202.7	327	315
Mississippi.....	5,110	4,356	731	—	23	205.8	244	235
West South Central	35,997	32,230	3,370	—	397	248.6	1,805	1,740
Arkansas.....	5,831	4,557	1,274	—	—	234.7	255	246
Louisiana.....	6,748	6,459	—	—	289	267.3	362	349
Oklahoma.....	7,403	7,355	—	—	48	339.8	412	397
Texas.....	16,015	13,859	2,096	—	60	215.1	776	748
Mountain.....	12,905	11,016	1,741	—	148	273.0	617	595
Montana.....	1,955	1,955	—	—	—	379.7	109	106
Idaho.....	1,073	1,073	—	—	—	225.1	60	58
Wyoming.....	1,346	618	728	—	—	265.6	35	33
Colorado.....	5,315	4,154	1,013	—	148	382.2	233	224
New Mexico.....	852	852	—	—	—	164.6	48	46
Arizona.....	938	938	—	—	—	182.6	53	51
Utah.....	1,059	1,059	—	—	—	188.5	59	57
Nevada.....	367	367	—	—	—	281.7	21	20
Pacific.....	39,032	34,630	2,364	578	1,460	341.9	1,939	1,870
Washington.....	7,560	6,880	653	—	27	387.4	385	372
Oregon.....	4,662	4,137	525	—	—	381.0	232	223
California.....	26,810	23,613	1,186	578	1,433	324.9	1,322	1,275

Number of patients taken from "Patients in Mental Institutions, 1942," Bureau of the Census, U. S. Department of Commerce, U. S. Government Printing Office, Washington, 1945.

\* Number of cases which would have been found if the prevalence rates had been the same as in State Hospitals in New York State.

\*\* Represents number of resident patients in State Hospitals per 100,000 of the estimated civilian population as of July 1.

TABLE 2

*Patients in institutions for mental defectives and epileptics at end of the year 1942, and estimated number of cases of pulmonary tuberculosis\* in these institutions in the United States, geographic divisions, and in each state*

DIVISIONS AND STATES	PATIENTS	ESTIMATED CASES OF PULMONARY TUBERCULOSIS*	
		Clinically Significant (2.4 per cent)	Apparently Healed (1.7 per cent)
United States.....	114,864	2,757	1,953
New England.....	11,949	287	203
Maine.....	1,082	26	18
New Hampshire.....	629	15	11
Vermont.....	375	9	6
Massachusetts.....	6,941	167	118
Rhode Island.....	813	20	14
Connecticut.....	2,109	51	36
Middle Atlantic.....	34,342	824	584
New York.....	19,966	479	339
New Jersey.....	5,782	139	98
Pennsylvania.....	8,594	206	146
East North Central.....	29,358	705	499
Ohio.....	7,550	181	128
Indiana.....	3,151	76	54
Illinois.....	8,985	216	153
Michigan.....	6,713	161	114
Wisconsin.....	2,959	71	50
West North Central.....	14,869	357	253
Minnesota.....	3,667	88	62
Iowa.....	3,405	82	58
Missouri.....	2,365	57	40
North Dakota.....	1,096	26	19
South Dakota.....	678	16	12
Nebraska.....	1,652	40	28
Kansas.....	2,006	48	34
South Atlantic.....	7,099	170	121
Delaware.....	463	11	8
Maryland.....	1,402	34	24
District of Columbia.....	641	15	11
Virginia.....	1,954	47	33
West Virginia.....	69	2	1
North Carolina.....	759	18	13
South Carolina.....	829	20	14
Georgia.....	454	11	8
Florida.....	528	13	9

TABLE 2—*Concluded*

DIVISIONS AND STATES	PATIENTS	ESTIMATED CASES OF PULMONARY TUBERCULOSIS*	
		Clinically Significant (2.4 per cent)	Apparently Healed (1.7 per cent)
East South Central.....	2,145	51	36
Kentucky.....	860	21	15
Alabama.....	843	20	14
Mississippi.....	421	10	7
Tennessee.....	21	1	—
West South Central.....	4,647	112	79
Louisiana.....	875	21	15
Oklahoma.....	248	6	4
Texas.....	3,524	85	60
Mountain.....	2,719	65	46
Montana.....	461	11	8
Idaho.....	545	13	9
Wyoming.....	391	9	7
Colorado.....	734	18	12
New Mexico.....	72	2	1
Utah.....	516	12	9
Pacific.....	7,736	186	132
Washington.....	1,819	44	31
Oregon.....	987	24	17
California.....	4,930	118	84

Number of patients taken from "Patients in Mental Institutions, 1942," Bureau of the Census, United States Department of Commerce, United States Government Printing Office, Washington, 1945.

\* Number of cases which would have been found if the prevalence rates had been the same as in State institutions for mental defectives and epileptics in New York State.

### Report of the Committee on Undergraduate Medical Education

Dr. Robert G. Bloch, *Chairman*

Dr. Harold M. Coon

Dr. C. Howard Marcy

Dr. Victor Johnson

Dr. H. McLeod Riggins

Dr. John M. MacMillan

Dr. Sidney J. Shipman

Dr. John H. Skavlem

During the years 1942 to 1945 the Committee investigated and reported on the teaching of tuberculosis in 18 medical schools; 13 institutions—5 in the East and 8 in the Middle West—were visited by the whole Committee, 5 on the West Coast by one member only. Although many of the shortcomings in the teaching in which the Society is interested could be laid to wartime conditions, the Com-

mittee realized that greater interest in the study of tuberculosis by undergraduate students was much to be desired. A plan evolved to stimulate the students' interests by the publication of a book written in popular style. One of the solicited manuscripts humorously illustrated in the style of *Huber the Tuber* was circulated among faculty members and students of a few medical schools; the response, as a whole, was unfavorable and further efforts in this direction were discontinued. In order to obtain a more complete overall picture of the state of teaching within a short time, the Committee resorted to the questionnaire method. Personal investigation had proved to be a slow and difficult procedure, especially in wartime, although by far the most thorough and informative one. The Committee was anxious to complete the investigative phase of its activities and to be ready with constructive suggestions at a time when improvements in medical education are under consideration throughout the country. The questionnaire was sent in full realization of the weaknesses of that method of investigation. The questions asked were based on the following chief considerations and principles which the Committee, by unanimous agreement, felt should guide the future efforts of the Society in working toward the improvement of undergraduate teaching.

(1) The students' interests can be stimulated most effectively through the efforts of his own teachers; in all instances where the subject is adequately presented by experienced and enthusiastic instructors, it is equally enthusiastically accepted by the students as a necessary part of their training. Therefore, it is thought best to turn the Society's attention to the stimulation of interest among deans and faculties in providing training through the medium of highly qualified teachers.

(2) The study of tuberculosis cannot be separated fruitfully from that of other pulmonary diseases. The teaching of the disease should be organized in conjunction with that in other pulmonary diseases from the standpoint of physical findings, clinical course, differential diagnosis and management. A real contribution can be made by encouraging the attitude not to consider pulmonary tuberculosis as a disease apart from others. The historical development of tuberculosis care—based chiefly on climatic consideration—has led not only to isolation of the disease but, to some extent, also of the tuberculosis specialist. The first step in correcting this situation should be to direct our efforts in teaching toward the field of all pulmonary diseases rather than of tuberculosis only.

(3) Such integration makes participation of general hospitals in the teaching mandatory. It will make education in pulmonary diseases part of the training in general medicine to a much greater degree than has been the case in the past, and the general hospital will emerge as the centre of teaching activities in this field as it is in any other. Tuberculosis sanatoria, which in the past have borne the chief load of instruction, will retain their great value as educational institutions, especially if they are located in the proximity of medical schools; the clinical experience of their staff members should be utilized fully for the benefit of the students.

Integration of the teaching of pulmonary diseases with that of internal medi-

cine cannot mean acceptance of the internist without special training in the field as a qualified teacher. The principle of academic teaching entitles the medical student to instruction by experts and investigators especially trained in any given field. In pulmonary diseases the general internist with a special knowledge of pulmonary diseases will be the most capable and inspiring teacher.

The questionnaire was sent to the 78 American and Canadian Medical Schools in November, 1945, and was answered by all of them. A full analysis of the considerable number of data gathered from the replies was studied by the Committee at its meeting on January 24, 1946, in Chicago<sup>4</sup> and was filed in the office of the Executive Secretary of the Society. A digest of the data concerning the teaching schedules of pulmonary diseases in general and the rôle of tuberculosis sanatoria in teaching is attached to this report in tables 1 and 2.

Although the figures show wide discrepancies in the total time allotted, as well as in the distribution of teaching through the various methods and facilities, the Committee gained the impression that, with relatively few exceptions, the total time allowed for instruction in pulmonary diseases, and particularly in tuberculosis, is adequate. It seemed that the chief problem is the most advantageous distribution of the available time with emphasis on the teaching in the general hospital and in out-patient departments.

Other data of interest were:

1: That 51 per cent of the schools are favored with a combination of teaching facilities consisting of general hospital, tuberculosis sanatorium and out-patient department.

2: That, in 78 per cent of the teaching affiliations of sanatoria with medical schools, staff members of the sanatorium hold faculty appointments, but that in only 60 per cent do they come to the premises of the medical school to teach.

3: That, by their own judgment, 60 per cent of the schools offer adequate training in thoracic surgery.

The following recommendations are submitted to the Council, after due deliberation and discussion:

(1) The original purpose of the Committee was to study and make recommendations on undergraduate instruction in tuberculosis. However, it is the consensus of the Committee that undergraduate instruction in tuberculosis cannot be and should not be separated from undergraduate instruction in acute and chronic pulmonary diseases.

(2) The Committee feels that its investigations thus far have demonstrated that, while the time allotted to undergraduate instruction in pulmonary diseases is adequate in most institutions, instruction in this field requires more improvement than is the case in other fields of comparable importance.

(3) The Committee recommends the integration of education in pulmonary diseases with instruction in all other phases of internal medicine and surgery. To this end, the Committee approves the principle of centralizing education in

<sup>4</sup> At the meeting the Committee was joined for the first time by its newly appointed member, Dr. Victor Johnson, Executive Secretary of the Council on Medical Education of the American Medical Association.

pulmonary diseases in medical teaching centres with general hospital facilities for the diagnosis and treatment of tuberculous and nontuberculous pulmonary diseases. This recommendation does not exclude the desirability of a connection between the medical teaching centre and the tuberculosis sanatorium.

(4) In view of the great importance of roentgenology, facilities in teaching institutions should include adequate X-ray equipment, access to X-ray records and the preservation of films to insure demonstration of the development of disease processes.

(5) Realizing that the success of any teaching program depends primarily upon the provision of enthusiastic and well trained teachers, the Committee suggests that the American Trudeau Society recommend to the National Tuberculosis Association that the latter undertake as a project the granting of fellowships in chosen medical schools for the training of teachers in internal medicine with special emphasis on pulmonary diseases.

(6) The Committee recognizes the fact that teacher training is a matter for the consideration of the Committee on Postgraduate Medical Education. However, the Committee feels that nothing is more important for the fostering of adequate undergraduate education than the procurement of competent instructors. The Committee would welcome an opportunity for joint discussion of this problem with the Committee on Postgraduate Medical Education.

(7) The Committee considers it desirable that a well rounded teaching program in the medical aspects of pulmonary diseases include instructions in the principles of chest surgery. The Committee would welcome the coöperation of the American Association for Thoracic Surgery in this regard.

(8) The Committee recommends the appointment of several deans of medical schools as members of the Committee.

TABLE 1  
*Summary of Teaching Schedules*

LECTURES .....	NUMBER OF REPLIES		NUMBER OF HOURS				AVERAGE	
	56		Maximum 53		Minimum 3		17.3	
	36 Expressed in		Number of					
	Hours	Weeks	Hours	Weeks	Hours	Weeks	Hours	Weeks
Hospital work (including sanatorium).....	28	8	320	8	6	1	49	3.2
Out-Patient work.....	30		144		1		28	
Hospital and Out-Patient work combined.....	6		60		18		38	
One school gives 3 weeks of combined instruction*								

Other schools stated that the training in pulmonary diseases is included in general medicine; some replies were still less definite.

\* Without details about the distribution of work during the week.



TABLE 2  
*Participation of Sanatoria in Teaching*

<i>Students in Residence</i>		<i>Day Visits</i>	
1 week.....	4	One visit (2 hours to all day).....	10
2 weeks.....	6	4 half-day visits.....	2
2½ weeks.....	1	7 half-day visits.....	1
3 weeks.....	1	18 half-day visits.....	1
4 months.....	1	Daily half-days for 2 weeks (or equiv-	
Period not given.....	1	alent).....	4
	—	Daily half-days for 4 weeks.....	2
	14	Daily half-days for 6 weeks.....	1
		Daily half-days for 8 weeks.....	1
		All day for 1 week.....	1
		2 hours weekly for 1 semester.....	1
		3 hours 3 times weekly for 1 month....	1
		Over 20 per cent of the whole study	
		period.....	1
		Undetermined.....	3
			—
			29
<i>Distance from Medical School</i>			
0 to 5 miles.....	29		
6 to 10 miles.....	10		
11 to 20 miles.....	4		
21 to 30 miles.....	1		
31 to 50 miles.....	6		
More than 50 miles.....	2		
	—		
	52		

## NOTICE

### United States Public Health Service Hospital Survey and Construction Act

With the signing by the President of the Hospital Survey and Construction Act, an appropriation of 375 million dollars is authorized during the next five years for the construction of hospitals and health centers. Three million dollars is also authorized for State-conducted surveys of need. These must be made preliminary to the granting of Federal funds for construction.

The Act provides latitude for each State to develop its own program of hospital and health center construction, to be administered by State authorities under standards specified by the United States Public Health Service. The Surgeon General will be assisted in establishing standards by a newly created Federal Hospital Council consisting of eight members to be appointed by the Federal Security Administrator.

"This Act sets for the first time a national policy which makes it clear that hospitals in the future must be planned, located and operated in relation to the overall health needs of the people," Thomas Parran, Surgeon General, U. S. Public Health Service, said. "This policy, as evolved through the leadership of hospital authorities of the country, is recognition of the integrated role that hospitals and health centers must play in the future. Adequate hospitals, health centers and related physical facilities are the essential workshops, without which it is not possible to provide even a minimum of modern health and medical services."

Any State may initiate action by submitting a request to the Surgeon General for funds to carry out an inventory of existing hospitals, and to prepare a plan for the construction necessary to provide adequate care for all the people. In making the request, the States must designate a single State agency to carry out the survey and planning and must appoint a properly qualified advisory council to consult with the State agency. The proportionate share for each State of the total Federal appropriation for survey and planning will be determined by the populations of the several States. However, Federal funds must be matched by two to one in defraying the survey expenses.

Allotments for the actual construction of facilities will not be made until the State plan based on the survey findings has been approved. Construction allotments to individual States will vary in amount. Population will be one factor, and in addition, the average per capita income will be used in the allotment formula in such a way that States with a lower per capita income, where there is relatively greater need for medical facilities, will receive proportionately larger allotments per capita.

Applications for funds for individual construction projects must be channeled through the designated State agency. Here again, Federal funds may not ex-

ceed one-third of the cost of a project. Before any single project is approved by the Surgeon General, sufficient evidence must accompany the building request to show that two-thirds of the total cost of construction is available from other-than-Federal sources, and that financial support is adequate for the maintenance and operation of the institution after completion.

## NOTICE

### United States Public Health Service Formation of a Division of Hospital Facilities

August 20, 1946

Formation of a Division of Hospital Facilities to assist Surgeon General Thomas Parran in carrying out the provisions of the Hospital Survey and Construction Act was announced today by the United States Public Health Service.

This division will absorb the functions of the Hospital Facilities Section of the States Relations Division, Bureau of State Services, which was abolished simultaneously with the creation of the Division of Hospital Facilities.

Headed by Medical Director Vane M. Hoge, the newly formed division of the Bureau of State Services will be responsible for carrying out the functions which the U. S. Public Health Service is authorized to perform in accordance with the provisions of the Act. This will include assistance to the States, their political subdivisions, and non-profit organizations in matters relating to the study, construction and operation of hospitals. The Division will also assist the Surgeon General in preparing regulations, determining allotments and grants and considering applications, plans and projects.



# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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**Mass Surveys.**—The mass chest X-ray survey has been a consistent part of the tuberculosis control program of the New York City Department of Health. Mass X-ray surveys and routine chest clinic examinations of the Department over the past ten years have reached an estimated half million individuals. The effectiveness and value of the mass survey is determined by the availability of facilities to classify promptly and properly the significance of the lesions found in the survey. This has been done by the Department of Health before a case is referred to a physician or to the district clinic. The Department of Health assumes the responsibility for all significant cases found. This responsibility may be shared with physicians or others so long as they are able to carry out the provisions of the Sanitary Code. In such cases, the Department requires biannual reports until such time as the case may be considered to be arrested. There have been three major objectives in the survey program: (a) to demonstrate the prevalence of disease according to age, sex, race and general economic status; (b) to demonstrate an efficient method of conducting a survey; (c) to stimulate the interest of others to set up within their own organization facilities to provide a regular periodic service. The first two objectives have been accomplished to a satisfactory degree. The third objective has been accepted and there is every reason to believe that in time an increasing number of organizations will assume their responsibility in this most important enterprise. (Author's Summary)—*Mass Survey in Tuberculosis Control*, H. R. Edwards, *New York State J. Med.*, February, 1945, 45: 269.—(P. Lowy)

**Fluorographic Survey.**—Because of the technical advances made in the field of fluorography, mass surveys are now practicable as a means of answering several pertinent questions relating to the pathogenesis and prognosis of pulmonary tuberculosis: (1) how many cases are discovered by mass fluorographic surveys that would otherwise possibly not have been discovered until later? (2) how many of the cases discovered have so-called "open tuberculosis" (3) how many would recover without treatment and how many are in need of medical attention? (4) how are the figures for these groups related to different ages and the two sexes? In coöperation with the Central Fluorographic Archive of the Swedish Navy, a survey was conducted of all personnel in the Navy for the two years 1941 and 1942. A total of 44,072 persons was examined, of which 1,209 (2.74 per cent) were found to show some suspicious type of markings in the fluorograph. No women were included in the study. Fluorographic classifications were divided into four groups: (1) doubtful pathological changes, (2) calcifications, (3) indeterminate activity, which included both active and not definitely healed lesions, as well as exudative pleuritis, hilar adenitis, pneumothorax, (4) cavitations. Of the 1,209 suspect cases, the following distribution among the four classes was made: Group 1: 9.0 per cent; Group 2: 30.0 per cent; Group 3: 59.3 per cent; Group 4: 1.7 per cent. These figures, when related to the original total of 44,072 men examined, show Group 1: 0.25 per cent; Group 2: 0.82; Group 3: 1.63; Group 4: 0.05. X-ray examinations of 91.3 per cent of all the positive cases revealed an 8.4 per cent error of overdiagnosis

by the fluorographic method in Group 1: 97.5 per cent agreement in Group 2, calcifications; 65 per cent agreement in Group 3 where a considerable range of interpretation would be expected by virtue of the nature of the group; and 95 per cent agreement in Group 4, cavitations. Clinical examinations were carried out on almost all positive cases, including sedimentation rate, sputum cultures, gastric lavage and temperature measurement. Bacilli were found in 0.31 per cent of all cases originally fluorographed, or 36.3 per cent of all cases examined bacteriologically. The sedimentation rate was above 10 mm. in only 27.9 per cent of the cases, while the temperature and weight changes were not significant. These findings would justify the conclusion that beside the X-ray findings, only the bacteriological examinations and the sedimentation rate have played any rôle as clinical signs among the fluorographically positive cases. Two-year follow-up of the patients revealed that 21 cases had become active; 5 formerly active cases were healed or inactive; 9 previously healed had become open; 35 previously open had become closed and 14 previously open had died of tuberculosis. These data would indicate that the risk of death for the fluorographically suspect cases is double the normal mortality for the corresponding age groups, whereas the mortality for the open cases discovered by the survey appears to be four times less than the average of open cases (based on Berg's survey in Sweden between 1928 and 1934).—*The Fluorographically Disclosed Cases of Pulmonary Tuberculosis and Their Early Prognosis*, A. Nelson, *Acta tuberc. Scandinav.*, 1946, Supplement XVI.—(P. Q. Edwards)

**Photofluorography.**—The object of mass chest examinations by the cheap method of photofluorography is not only the discovery and treatment of the individual case of tuberculosis, but also the closing off of the source of infection. The present work began in 1939, and was the result of a concerted attack on the disease by physicians, the state, the army, social service institutions and industry. In Zürich canton 15,447 were filmed, of which

5,931 were workers, 2,066 school and hospital personnel, 1,058 state personnel, 864 patients in hospitals, sanatoria and insane asylums and 5,528 soldiers. A roentgenologist, X-ray technician and assistant operate the machine and read the films, helped by four assistants from the organization being filmed. The findings are indexed according to a special key, and classified into absolutely important, relatively important and insignificant. All those with suspicious chest findings are referred for further work or 'clarification'. The general medical practice is used for this, and the patient may choose anyone he wishes. In cases of tuberculosis the problems that are handled are: medical treatment of the patient; care for the family, especially economically; and care for the patient after medical care is completed, including finding an appropriate job.—*Die Schirmbildphotographie*, H. R. Schinz & F. Kollbrunner, *Schweiz. med. Wchnschr.*, October 18, 1945, 75: 897.—(J. Gerstein)

**Tuberculosis in Tropics.**—Although exact figures are not available, observers agree that the incidence of tuberculosis among the natives of British West Africa is high. Under the circumstances, hospital admissions naturally do not reflect the actual incidence of the disease; but it is worth mentioning that in the Gold Coast one in every nine hospital deaths is due to tuberculosis. Post mortem examinations reveal that the bronchopneumonic and miliary forms of tuberculosis are most common, with acute cavitation and little evidence of fibrosis. Primary foci are not uncommonly found. A comprehensive program for the control of tuberculosis under the prevailing primitive conditions is outlined.—*Tuberculosis in British West Africa*, R. B. Wellesley Cole, *Bull. Nat. A. Prevention Tuberc.*, Great Britain, February, 1945, p. 5.—(P. Lowy)

**Tuberculosis in Deaconesses.**—The mortality in deaconesses caring for the sick is 1.2 per cent, the same as in the general population. Of these, 21 per cent died of tuberculosis, as compared with 6.1 per cent in the general population. Pirquet tests and X-ray films are

taken on beginning work, and every six months for three years, then every year. Only persons with positive Pirquet tests are placed on tuberculosis service. Fifty-two per cent reacted positively at the onset, and 92 per cent after four to five years. Of 66 with changing Pirquet tests, 16 had clinically apparent disease and 2 died. The mortality and morbidity among children with changing Pirquet tests is even higher. Among 52 who began work with positive Pirquet tests, there were 3 cases of tuberculosis, all mild. It is recommended that all nurses be radiographed every six months until the age of thirty-five, and that all those not reacting to the Pirquet test, especially if young, be vaccinated with BCG.—*Diaconesses et tuberculose, E. Urech & P. Rochat, Schweiz. med. Wchnschr., June 9, 1945, 75: 504.*—(J. Gerstein)

**Primary Tuberculosis.**—The authors refer to Rich's premise that acquired resistance to tuberculosis in the human is on the bases that (1) the establishment and subsequent arrest of the primary complex are seldom followed by the occurrence of similar lesions despite opportunities for extraneous infection, and, (2) primary lesions characteristically undergo regression. The evidence that lesions of the primary complex are arrested or "healed" and hence are unlikely to contain living tubercle bacilli is based on histological studies, and on inoculation of material from lesions of the primary complex into guinea pigs. Young Ghon tubercles have been shown to contain many stainable acid-fast bacilli, while older lesions yield no or only a small number of viable bacilli on animal inoculation. Infants with primary infection are more likely to suffer from infection beyond the limits of the primary parenchymal lesion and adjacent nodes with subsequent death. Therefore, it appeared important to determine how frequently tubercle bacilli could be demonstrated by animal inoculation in the primary complex of children dying from nontuberculous causes. Twenty-nine cases were studied over a six-year period. Some specimens were obtained locally and some by mail. About half the specimens had

been packed in borax. From each parenchymal lesion suspensions were prepared for subcutaneous inoculation of 2 guinea pigs. Other preparations were made from hilar lymph nodes. In 20 cases only parenchymal lesions were available. In 7 instances hilar nodes as well as parenchymal material were received. In 2 cases the disease had been limited to the hilar nodes. Unless they died sooner, guinea pigs were killed and autopsied at eight weeks. The youngest child in whom virulent bacilli were found was 3 months of age, while the oldest was 11 years. In only 5 of the 29 cases were tubercle bacilli demonstrated. If, as seems likely, the primary complex in most instances tends to become sterile during the early months or years, then the primary infection is usually a benign disease when the environment is good. So long, however, as viable tubercle bacilli exist they must be regarded as potential instigators of the reinvasion type of pulmonary tuberculosis. Cellular reactions or other morphological evidence of activity of a tuberculous lesion can seldom justify more than a presumption that the lesion contains viable tubercle bacilli, especially if the lesions are encapsulated, fibrotic, caseous or calcified. It is regrettable that no knowledge is available regarding the tuberculin reactions in this series. Many have suggested that, as the primary complex becomes encapsulated and finally inactive, previous sensitivity to tuberculin may diminish or be lost. Failure to demonstrate living bacilli in 24 of the 29 children supports the belief that tuberculin sensitivity in children may be transitory and that, in children whose tuberculosis is limited to the primary complex, the continuation of sensitivity to tuberculin is probably related to the infectivity of the tuberculous focus. It is logical to assume that foci which no longer contain viable bacilli will eventually cease to maintain sensitivity. Loss of this sensitivity does not necessarily mean loss of immunity. Norwaal, in a study of 112 children with a Ghon complex, found between one-quarter and one-fifth negative to the second strength of PPD, indicating that, as in this series, probably there was no longer any antigen being



absorbed from the tuberculous lesions and, therefore, viable bacilli were no longer present. In such cases it seems unlikely that the adult type of tuberculosis could develop except by reinfection. Follow-up on negative reactors with a Ghon complex might help to determine whether such healed infection renders a person living in a tuberculous environment refractory to the disease, produces a second primary complex or eventually produces the adult type of tuberculosis. If the results of this study are a true reflection of the infectivity of the lesion of the primary complex in children without concomitant other tuberculous disease, one may conclude that the tubercle bacilli responsible for primary lesions in childhood tend, in most instances, to become avirulent or disappear.—*Infectivity of the Primary Complex of Tuberculosis of Childhood*, W. H. Feldman & H. F. Helmholz, *Am. J. Dis. Child.*, October, 1945, 70: 201.—(K. R. Boucot)

**Primary Tuberculosis.**—Tuberculous infection is most dangerous in infants, and the prognosis in this age group is least favorable. In older children the infection is usually benign. Calcification and healing of the primary complex and of the involved mediastinal nodes is the rule, and the child is ready for discharge from the sanatorium in six to twelve months. In a certain number of cases, however, evidences of continued activity persist. The temperature remains slightly or intermittently elevated, the sedimentation rate remains rapid, and the child does not thrive properly. Such children are subject to late complications, such as development of bone lesions, cervical adenitis and pleural effusions. It is doubtful that tuberculosis of such a progressive nature is due to a large initial infection dose. It seems more likely that active tuberculous foci persist in partially calcified mediastinal nodes, or that local and hematogenous spreads occur from an unhealed lung focus. The prognosis of children in whom primary tuberculosis causes a long illness is probably poor.—*Primary Tuberculosis in Children Causing Long Illness*, J. V. Hurford, *Lancet*, November 17, 1945, 246: 624.—(H. Marcus)

**Hilar Shadows in Children.**—The author has examined more than a thousand juvenile contact cases. Five per cent of these children presented definite proof of tuberculous infection. The mere presence of hilar shadows was not considered proof of glandular disease as in children, the pulmonary vessels are relatively large and overshadow the lymph nodes. The majority of the shadows near the mediastinum and the heart border are not glandular shadows. The paratracheal and tracheobronchial lymph nodes on the left are obscured by the heart shadow. In childhood tuberculosis, the primary pulmonary lesion is found generally at the level of the interlobar fissure. Shadows near the border of the heart very seldom represent tuberculosis but mostly a mild pulmonary infection. Only massive tumor formation of the mediastinal nodes will give X-ray evidence. These are generally hopeless cases. In the majority of the cases of childhood tuberculosis, the glandular involvement can not be detected on X-ray films. It is probable that the glandular lesion, which every child must have had, as 97 per cent of the adults show calcifications, is too small to be seen on the X-ray film. As long as the hilar shadows do not show any gross deformity there is no reason to suspect a primary tuberculous infection. But even if the hilar shadows are enlarged and deformed, they may not be of tuberculous origin, especially if they are situated in the lower portion of the hilum. In this case the Mantoux test will give further information. In less than year old infants a positive Mantoux test is proof of tuberculous infection. After two years a positive reaction indicates only the degree of allergy of the child. The author has examined a number of children with unquestionable primary infection. Some of them showed, on a later examination, only slight enlargement of the hilar nodes but no other characteristics. These are considered as entirely healed cases of primary tuberculosis. It is emphasized that hilar shadows without special characteristics are very frequent in children and are not of any pathological significance.—*Consideraciones sobre las imágenes hiliares en el niño*,

A. Telo, *Rev. med. peruana*, June, 1945, 18: 230.—(W. Sienkoff)

#### Sensitivity to Tuberculin and Prognosis.—

The present study was undertaken to test the theory that, in the absence of overwhelming disease, the prognosis of tuberculosis in young children is related to the degree of their hypersensitivity to tuberculo-protein. The material for the study was drawn from the records of children followed in the Tuberculosis Clinic of the Harriet Lane Home. The criteria for admission to the clinic demand that the child be less than two years of age and that he be either infected with tuberculosis, as demonstrated by a positive tuberculin test, or known to be exposed to sputum-positive tuberculosis, and therefore in unusual danger of becoming infected. In the routine operation of the clinic, children are tested with tuberculin, and X-ray films of their chest are taken upon admission. Both procedures are repeated at intervals thereafter, and about once each year after the acute stage of their disease is passed. Old Tuberculin was used exclusively for skin testing, starting with 0.001 or 0.01 mg. of tuberculin, the dose being increased, if negative, up to and including 1.0 mg. All tests were performed by the intracutaneous injection of 0.1 cc. of solution. The group under study consisted of 207 children, all tuberculin-positive. There were nearly four times as many Negroes as whites. There were 5 more males than females in the whole group. All patients followed for a period of less than two years have been discarded from this study, with the exception of those who died. The maximum period of follow-up was seventeen years, the mean period being approximately eight years. Thirty-four reacted to not less than 1.0 mg. of tuberculin. Nineteen (56 per cent) of these subsequently lost their hypersensitivity and did not regain it during the period of study. None of these 34 children showed demonstrable parenchymal lesions of calcification on X-ray films of the chest; none developed extrapulmonary tuberculosis and none died. Twenty-six reacted to 0.1 mg. of tuberculin. Six (23 per cent) of these subsequently lost

their sensitivity to this dose and did not regain it. Only one of the 26 had parenchymal involvement and 3 showed subsequent calcification on chest roentgenograms. Two had extrapulmonary tuberculous manifestations of the disease; none died. In the highly sensitive group, 103 children reacted positively to the 0.01 mg. dose and 44 gave vesiculated reactions to 0.1 mg. Of those positive to 0.01 mg., 43 per cent had non-calcified parenchymal lesions, 62 per cent of the 103 developed intrathoracic calcifications, 25 per cent had manifestations of extrapulmonary tuberculosis, 14 per cent died, 12 per cent had no evidence of tuberculosis apart from a positive tuberculin test. Of the 44 giving vesiculated reactions to 0.1 mg., 50 per cent had parenchymal lesions, 77 per cent developed intrathoracic calcifications; 27 per cent had extrapulmonary manifestations of the disease, 16 per cent died, 12 per cent had no evidence of tuberculosis except for a high degree of sensitivity to tuberculin. No child in the markedly hypersensitive group sustained a persistent loss of sensitivity to the 0.01 mg. dose of tuberculin. According to this study the prognosis for children under three years reacting positively to not less than 1.0 or 0.1 mg. of tuberculin (except in overwhelming disease or in a very early stage of the infection) was good, in sharp contrast to those children who were highly sensitive where the prognosis was bad. The degree of hypersensitivity was closely related to the extent of the tuberculous lesions.—*The Relation of the Degree of Sensitivity to Tuberculin to the Persistence of Sensitivity and to Prognosis in Young Children*, Lydia B. Edwards & Janet B. Hardy, *Bull. Johns Hopkins Hosp.*, January, 1946, 78: 13.—(J. S. Woolley)

#### Pleural Reaction in Primary Tuberculosis.

—The demonstration of pleural effusion in primary tuberculosis of the lungs is not common. This is felt to be due to inadequate methods of routine examination. The method devised by Laurell permits demonstrating small pleural exudates by radiography. Examination of the recumbent patient with horizontal X-rays demonstrates with greater

clarity the presence of small effusions. By alterations in position of the patient and apparatus as described by Laurell, smaller effusions and more delicate detail can be studied. The authors recognized effusions of 3 to 5 ml. by methods which are improvements of the original technique of Laurell. The question as to whether primary tuberculous infection of the lungs can be roentgenographically differentiated from certain types of post-primary infections is briefly discussed. No other type of tuberculosis of the lungs is associated with such a powerful hilar reaction as primary tuberculosis. Ten cases are reported and in 9 of these the presence of a pleural exudate on the homolateral side of the infection could be demonstrated radiologically; this fluid was demonstrable only with the patient in the recumbent position. The quantity of fluid varied from 7 to 150 ml. There seemed to be a relation between the quantity of fluid and the length of time that had elapsed between the onset of the disease and the examination of the patient. Those appearing early in the course of the disease presented the largest exudates. Apparently there is a rapid absorption in such types of pleurisy, as shown by the fact that patients seeking treatment a week after the onset did not present large exudates. Examination of the fluid obtained by thoracentesis in primary tuberculosis of the lungs revealed an increase in the albumin content above the normal of 3 per cent and an increase in the cell count above the normal of 5,000 per cc. but seldom above 10,000 per cc. Differential counts reveal mononuclear cells predominating in normal fluid and polynuclear cells predominating in the exudates of primary tuberculosis, at least in the initial or acute phase. In primary tuberculosis of the lungs the demonstration of pleural exudates indicates that the disease is in an acute stage though clinical signs and symptoms be lacking. A pleural exudate may exist before parenchymal changes in the lung are demonstrable radiographically.—*The Reaction of the Pleura in Primary Tuberculosis of the Lungs*, R. Muller & S. Lofstedt, *Acta med. Scandinav.*, September 26, 1945, 122: 105.—(E. R. Loftus)

**Minimal Tuberculosis.**—The study is based on 100 cases of minimal pulmonary tuberculosis conforming to the N. T. A. classification. Only those cases were included which had had at least two years' observation. There were 42 females and 58 males. The age range was as follows: 47 between 15 and 25 years, 40 between 25 and 35 years, 13 over 35. This age distribution is as anticipated because Chilean morbidity from tuberculosis is highest in the 20 to 30 year old age group. Six were private patients and 94 were insured workers, either civil servants, private employees or journalists. The sputum studies included culture and animal inoculation in all but 14 cases: 33 per cent had positive sputum or gastric contents at the beginning of the study. Of these, 30 were converted and remained negative for at least two years. Conversion took place in six months to one year, except in one instance in which sputum remained positive for three years. Subjective symptoms in the 33 initially positive cases were present in 28 or 84.4 per cent. They consisted of weight loss, cough, expectoration, toxemic and dyspeptic manifestations, hemoptysis and back-ache. Of the 67 initially negative patients, 18 or 26.8 per cent subsequently became positive. Among 49 patients who were never positive, 33 cases of manifest activity occurred during the five-year study. Of these 33, 23 tended to improve and 10 to progress. In this latter group, persistent search by culture and inoculation failed to yield positive results in 16 cases. Of the 18 initially negative cases that subsequently became positive, one showed no change in the lesion, 3 progressed favorably and 14 unfavorably. Appearance of bacilli in the sputum almost invariably coincided with spread. Of 33 initially positive cases, 10 or 30.3 per cent underwent spread. Of 67 initially negative cases, 24 or 35.8 per cent also underwent increase in their lesions. Therefore, the finding of bacilli in cases of minimal pulmonary lesions has no prognostic significance. Forty-seven patients had normal sedimentation rates, while 53 had increased rates. Of the 47 with normal sedimentation rates, 9 remained stationary, 15 underwent exacerbation.

tion, and 29 showed subsequent improvement. Therefore, this group had an unfavorable course in 28.3 per cent. No pleurisy was observed in this series. Cases with normal sedimentation rates have a less favorable evolution than those with an initially elevated rate. The sedimentation rate does not have a high prognostic value in minimal tuberculosis. Collapse therapy was used only when there was an unfavorable course, especially in those cases where cavity formation occurred. When lesions were exudative in appearance, the patients were placed in sanatoria on a strict rest regimen. Recovery was gauged by stability for a minimal period of two years. This occurred in 40 patients who underwent rest cure at home, 19 who underwent rest cure at a sanatorium and in 14 cases treated by pneumothorax. Of the unfavorable cases, 11 were on rest cure at home, 8 on rest cure in a sanatorium and 6 had pneumothorax. There were 2 deaths in this group. An exact appraisal of therapy is not possible because of changes and combinations of therapy. Abnormal physical signs were present in only 11 cases. They consisted of changes in resonance, vesicular murmur or fine râles. Contact histories were reliable; 37 were contacts to patients with a positive sputum, 18 of these had had heavy exposure through contacts with parents, brothers or spouses.—*Analysis of 100 Cases of Minimal Tuberculosis*, H. O. Puelma & G. Grebe, *Dis. of Chest*, September-October, 1945, 11: 375.—(K. R. Boucot)

**Cavity Closure in Tuberculosis.**—Four cases of pulmonary tuberculosis that came to autopsy are presented, with proof that occlusion of the bronchus draining a cavity precedes closure of the cavity. It is also felt that such bronchial occlusion is the essential and main factor in certain healing of cavities.—*Kavernenschlund und Verschluss der Kavernenbronchien*, W. Berblinger, *Schweiz. med. Wchnschr.*, October 27, 1945, 75: 941.—(J. Gerstein)

**Rheumatism and Tuberculosis.**—Tuberculosis of the joints occurs in many forms. It may vary from an acute inflammation of sev-

eral joints (type Bouillaud) to a chronic deforming arthritis (type Charcot). Tuberculous rheumatism is a pathological entity proven more and more frequently by obtaining cultures of tubercle bacilli on Loewenstein's medium. The following case histories of tuberculous rheumatism are given: (1) In a 23 year old man with fibrocaceous pulmonary tuberculosis conversion of sputum was achieved by a two-stage thoracoplasty. The patient developed pains in several joints, without swelling, which were resistant to salicylates. (2) A 23 year old man whose family history revealed several cases of tuberculosis was observed. Since the age of eleven he had complained of pains in various joints without swelling. At the age of twenty-two he started to have pain in his spine and to develop a marked kyphosis. A chest roentgenogram showed diffuse clouding of both apices. The gastric juice contained acid-fast bacilli. (3) A 16 year old boy with acute polyarthritis was seen, who had had similar attacks at the age of eight and eleven. A chest roentgenogram revealed no abnormalities, the gastric juice was negative for tubercle bacilli, a patch test was positive. Examination of the heart showed numerous premature beats. The knees and the right elbow were swollen and painful. Fluid withdrawn from the left knee contained tubercle bacilli. The disease was not influenced by the administration of salicylates.—*Rhumatisme et tuberculose*, R. Desmeules, L. Rousseau & Ph. Richard, *Laval méd.*, January, 1946, 11: 35.—(G. C. Leiner)

**Chronic Miliary Tuberculosis.**—The problem of chronic miliary tuberculosis brings forth the questions as to whether this condition really exists and, if so, by what origin, and in what way eventual healing can be explained. Secondly, the problem arises of the differential diagnosis from lung conditions having similar roentgenological appearance. These include miliary carcinosis, coniosis, multiple pyemic small abscesses, leukemic infiltrations of miliary form, disseminated influenzal pneumonia and bilharziosis of the lungs. Two other diseases which have very similar radio-

logical appearances are: first, the idopathic progressive brown induration of the lung where the minute spots seen in the film are due to hemosiderosis caused by recurring hemorrhage; and second, the diffuse myomatosis or fibrosis of the lung with formation of cysts. In the second condition, which shows a relation to tuberous sclerosis, the small cysts may not be apparent in the ordinary roentgenogram but may be clearly apparent in tomographic films. The differentiation of chronic miliary tuberculosis and these last two mentioned conditions is reportedly not difficult, but more difficulty is encountered in distinguishing chronic miliary tuberculosis from pulmonary congestion, Besnier-Boeck's disease and tuberculous broncho-pneumonia with confluent foci. It appears necessary to establish severe criteria in the diagnosis of chronic miliary tuberculosis. These include positive tuberculin tests; history of contact; if possible, the presence of tubercle bacilli in gastric lavage or sputum; extrapulmonary foci that could arise only by blood stream dissemination; the presence of foci of about the same size in both lung fields and the uniform dissemination of these foci. Fourteen cases of chronic miliary tuberculosis are reported. They occurred in children above two years of age. Most of these have shown extrapulmonary involvement which could be explained only on the basis of blood stream dissemination. Tuberculin tests in all cases were positive. Tubercle bacilli were demonstrable in the gastric lavage or sputum of 8 of these cases. Different hypotheses have been suggested by various authors to explain chronic miliary dissemination. Many investigators have remarked that due attention should be given to the reaction of the lymphatic system in judging a hematogenous dissemination, because such dissemination originates rather often from caseated lymph nodes. One must also consider the fact that hematogenous dissemination is often followed by involvement of the lymph vessels and that the clinical picture of a lymphangitis resembles that of chronic hematogenous tuberculosis. Another hypothesis assumes that in the explanation of the chronic

course of a miliary tuberculosis the quantity of the disseminated tubercle bacilli in the blood stream and the repetition of this dissemination are of greatest significance. An argument in favor of this hypothesis, assuming that the hematogenous seeding occurs but once or, if recurring, spills very small numbers of organisms, is the relatively rare occurrence of meningitis. Broadening of the upper mediastinal shadow was observed in the majority of cases, both lethal and non-lethal cases. In those instances in which post mortem examinations were made, there were large caseated paratracheal lymph nodes. In acute miliary tuberculosis massive quantities of tubercle bacilli enter the circulation and the filtration by the lung is ineffective, but in those instances in which the dissemination occurs but once the filtration by the lung is effective. There are exponents of the argument that chronic miliary tuberculosis results from the dissemination of dead or attenuated tubercle bacilli. This hypothesis is strengthened by the number of cases which are accompanied by lupus. If it is accepted that papulonecrotic tuberculids are caused by bacilli of decreased virulence, then the arguments for dissemination of attenuated bacilli is further enhanced, for the occurrence of tuberculids has been repeatedly observed in chronic miliary tuberculosis.—*Chronic Miliary Tuberculosis*, S. van Creveld & G. J. Huet, *Acta med. Scandinav.*, February 12, 1948, 113: 185.—(E. R. Loftus)

**Atypical Tuberculosis and Sarcoidosis.**—There are indefinite transitions in the clinical as well as pathological-anatomical manifestations of tuberculosis. This is seen in the acute septic form at one extreme, the usual exudative-productive as the commonest form and the atypical chronic miliary tuberculosis at the other extreme. The concept has gradually developed that these morphologically different manifestations are due to a different manner of reaction on the part of the cells and to the different sensitivity of these cells to the tubercle bacillus and its products. This sensitivity varies extremely, first from individual to individual, second from organ to organ and fi-

nally, from time to time in the same individual. The question as to whether immuno-biological or other factors determine a manner of reaction which causes atypical forms of tuberculosis, leaves two theoretical possibilities as answers. Clinically, there may be still more malignant forms than the pneumonic and, conversely, there may exist specific benign forms with pure productive changes and especially strong tendencies to recover. In the first instance, specific references are given to the so-called acute atypical miliary tuberculosis which occurs without obvious macroscopical findings and makes its appearance under the picture of lymphatic leukemia. At the opposite extreme are those cases of chronic miliary tuberculosis which have in some instances been cured and those related or identical processes that assume yet another form. Histologically the resemblance of Boeck's sarcoid to tuberculosis is so great that on the whole the two kinds of changes cannot be distinguished from one another. In particular there is no distinction between extremely chronic miliary tuberculosis and Boeck's sarcoidosis. The failure to find tubercle bacilli by any means in sarcoid tissue and the general anergy to tuberculin are the main factors that place sarcoidosis on a nontuberculous basis. But the tuberculin reaction is not always positive in tuberculosis and a significant percentage of negative tuberculin reactions occurs in chronic miliary tuberculosis. The etiology of the disease must be determined by biopsy or post mortem examination. The characteristics of Boeck's sarcoidosis are its extremely chronic course and its tendency to fibrous changes and healing, exactly in the same way as is seen in the most chronic miliary tuberculosis. In the opinion of this author, anyone who can draw a sharp line between chronic miliary tuberculosis and classical tuberculosis on one hand and Boeck's sarcoidosis on the other, draws positive conclusions on negative premises. The author also states that histological examination of excised tissue, reportedly from cases of Boeck's sarcoidosis, revealed very small, acid fast, round or oval bodies scattered in the epithelioid tissue. The significance of these

bodies is at present unknown.—*Atypical Tuberculosis—Boeck's Sarcoid*, R. Opsahl, *Acta med. Scandinav.*, March 18, 1943, 113: 267.—(E. R. Loftus)

**Mediastinal Dislocation following Pneumothorax.**—A 35 year old female was seen with severe dyspnea, cough, wheezing in the chest, sputum positive for tubercle bacilli. She had had pulmonary tuberculosis since 1932. A right pneumothorax had been induced in 1937 and abandoned after four years. The lung, however, did not reëxpand and roentgenological examination in 1944 showed displacement of trachea, heart and mediastinum to the right and elevation of the right diaphragm. An upper stage, three-rib thoracoplasty with apicolysis was done on the right side, which allowed the trachea and heart to return to an almost normal position. Two days after the operation there was considerable improvement in the patient's breathing.—*A Case of Extreme Mediastinal Dislocation Complicating Tuberculosis*, W. L. Phillips, *Clin. Proc. (Cape Town)*, October, 1945, 4: 459.—(G. C. Leiner)

**Readhesion after Intrapleural Cauterization.**—Three forms of obliteration of the pneumothorax space are mentioned: (1) The acute obliteration resulting from loss of air through cannula tract. While positive intrapleural pressure engendered by severe post-operative coughing or vomiting are most frequently responsible, in some cases endobronchial tuberculosis may be a factor by producing a check-valve type of bronchial obstruction that result in rapid reëxpansion of the lung. (2) Secondary obliteration of areas recently separated by the pneumonolysis occurs within a week or two of operation. (3) Late obliteration, the sequel of postoperative effusion. This is outside the scope of this paper. The factors aiding readhesion are chiefly the presence of raw exuding cauterized surfaces, particularly projecting stumps, traumatic pleuritis or blood. In some cases the pleura is covered with a fine pellicle of organized lymph which adheres readily if two surfaces are allowed to come into

contact. When any deposit of fibrin, lymph or blood occurs on the pleura the coagulum is invaded by connective tissue elements. Hence vascular recent adhesions, rich in capillaries, springing from an actively inflamed visceral pleura, are the ones, after division, most likely to readhere when given a chance. The incidence of this complication is about 3 per cent of reported cases. The prevention of readhesion is accomplished by judicious use of premedication to avoid postoperative vomiting; avoidance of prolonged operative sittings; careful massage, closure and compression of cannula puncture wounds; sedation of cough after operation. Frequent fluoroscopic examinations to ensure adequate lung collapse are essential. It is better to keep the lung well collapsed for some weeks after section of adhesions to allow full retraction of severed tissues and maximum benefit from the operative procedure. To this end attention to posture in the ten to fourteen days after surgery is of great importance, particularly in cases where the lung collapse is unsatisfactory, the pleura inflamed, operative trauma extensive and when cauterization is followed by effusion. The lung becomes fixed most easily to that part of the thorax where there is the least respiratory movement—usually to the posterior parts; hence during fluoroscopy particular attention should be given to the costo-vertebral gutter. In treatment, the attempt to break down obliteration by frequent refills is first, but often unsuccessful. In these cases reoperation should not be long delayed. The author reports seven cases; in five reoperation was done immediately. There was usually direct readhesion between the visceral and parietal pleurae in addition to readhesion of stumps. Long slender newly formed bands or sheets were rarely found. In early reoperations it was possible to separate the readherent stumps and pleurae by blunt dissection. The outer layer of the readhesion was invariably the densest part. When granulation tissue was encountered, in cases done after a longer interval, detachment was still possible but accompanied by considerable parietal oozing. In one of the author's cases tuberculous empy-

ema followed, and in another a persistent pleural effusion developed.—*Readhesion after Intrapleural Cauterization*, R. J. C. Maxwell, *J. Thoracic Surg.*, June, 1945, 14: 194.—(W. M. G. Jones)

**Oils in Disinfectant Oleothorax.**—If tubercle bacilli persist, with or without varying degrees of purulency, approximation of pleural surfaces is ultimately demanded. The empyema cavity becomes of more immediate importance than the lesions in the underlying lung, not only because of the toxemia produced by the empyema, but also because the extent of the surgery necessary for the lung lesions is generally less formidable than that required for the empyema. Many drugs and solutions have been used in the treatment of tuberculous empyema, but all with indifferent success. Matson, in 1932, reported 60 per cent satisfactory results in 50 cases of empyema treated with gomenolized oil. Others have used 4 per cent cottonseed oil with similar results. Empyema always results from caseation and ulceration of subpleural tuberculous foci. The greater incidence of both serous effusions and empyema in mechanically unsatisfactory pneumothoraces is explained by the fact that the adhesions which prevent collapse and the effusion or empyema are themselves caused by subpleural tuberculous foci. Following Matson's suggestion, the authors used both cod-liver oil and peanut oils because of their irritating effects on the pleura. As chemical disinfection of an infected and constantly reinfected pleura is considered impossible at present, irritant oils act beneficially by producing an inflammatory reaction which walls off the subpleural focus, prevents the constant reinfection of the pleural surfaces from this focus and encourages pleuritis which may eventually obliterate the empyemal space. Moreover the oils inhibit the growth of tubercle bacilli and markedly reduce the toxic effects of the tuberculous infection. The immediate symptomatic reaction to oleothorax is most marked in patients with a mild infection, and least marked in those with a very purulent empyema. Within from four to eight hours after instillation of the first unit of

oil (usually 50 cc.; subsequently larger amounts are used according to reaction) there will be pain in the chest which rarely persists more than forty-eight hours. There is also some malaise and a mild temperature reaction. The toxemic symptoms of empyema rapidly and at times dramatically disappear within a few weeks by which time the fluid in most cases has become thin. Occasionally the fluid though scanty remains purulent but even these patients were symptom free. This improvement is followed by increase in general well-being and return of appetite and a gain in weight. These patients become a much better surgical risk should surgery be necessary. The authors treated 20 patients: 6 of these re-expanded their lungs without requiring thoracoplasty; of the remaining 14, 10 now have oleothoraces which are negative for tubercle bacilli. In the conduct of oleothorax the authors stress the necessity for frequent examination of the patient with periodic removal of pus or fluid and the maintenance of negative intrapleural pressures to avoid extension of infection or oil along needle tract or development of bronchial fistula.—*Studies in Oleothorax: II. The Use of Oils in Disinfectant Oleothorax and in the Re-expansion of the Lung in Tuberculous Empyema*, P. D. Crimm & J. J. Westra, *J. Thoracic Surg.*, August, 1945, 14: 270.—(W. M. G. Jones)

**Closed Extrapleural Pneumonolysis.**—This is a report of 50 operations in which some degree of extrapleural dissection was performed. These cases represent 35 per cent of 143 intrapleural pneumonolyses. In all these cases the attachments were considered unsuitable for division by the accepted criteria for intrapleural pneumonolysis, yet a satisfactory collapse was obtained in 35 or 70 per cent of them by extrapleural dissection technique. If the 13 operations performed for exploratory purposes in doubtful cases are excluded, the operation was successful in 31 out of 37, or 84 per cent. Twenty-six cases had no postoperative fluid. Large postoperative bleeding followed in 3 of the patients who had partial dissection (23 per cent) and in 3 others. There were 6 cases

of empyema, 5 being tuberculous, (10 per cent). Regarding technique, the Coryllos thermal cautery unit was used in all cases. In preparation for extrapleural dissection the pleura was elevated with 1 per cent novocain and the pleura incised one to 2 cm. from the lung. The extrapleural separation was carried out with the aid of a new type of sponge carrier and dissector designed by the author (made by the American Cystoscope Makers). Bleeding was controlled by the cautery, which was also used for dense fibrous strands. Small amounts of blood were wiped away by the dissector, larger accumulations being aspirated by means of a long suction tube. The presence of tubercles on the lung was considered to be no contraindication to extensive stripping if there were several centimeters from area of division. If they were on the parietal pleura the operation was not attempted. There are 4 illustrative case reports.—*Closed Extrapleural Pneumonolysis*, J. S. Conant, *J. Thoracic Surg.*, October, 1945, 14: 369.—(W. M. G. Jones)

**Death Due to Pneumoperitoneum.**—The case is reported of a 48 year old patient who was to be treated with pneumoperitoneum for tuberculosis of the right upper lobe. The induction of the pneumoperitoneum was uneventful. At the second refill the needle was introduced cautiously into the abdominal wall, two fingers to the left and below the umbilicus. At first the manometer showed no oscillations and there was no passage of air. The needle was introduced somewhat deeper, whereupon 300 cc. of air went in rather easily. This was followed by sudden cough, general malaise and respiratory distress. The needle was withdrawn. A few minutes thereafter generalized convulsions of short duration set in. Coma developed and the patient died twenty to twenty-five minutes later. Autopsy revealed a hematoma in the rectus muscle. No injury of a major vessel could be found. The peritoneum showed no evidence of puncture. The intestinal loops were normal. Section of the heart revealed the blood to be foamy. The



brain was normal in appearance. There was tuberculosis of the right upper lobe and some edema of the left lung. The cause of death was attributed to air embolism in the lungs and possibly air embolism of the brain.—*Accident mortel au cours du pneumopéritoine, G. Roche & J. Giron, Rev. de la tuberc., 1944-1945, No. 7-9, 9: 102.*—(V. Leites)

**Thoracoplasty Binder.**—This is a description, with good pictures, of the thoracoplasty binder which has been in use at Herman Kiefer Hospital for the past ten years. Binders are applied ten days after the second and succeeding stages of thoracoplasty and are kept on between operations and afterward until the chest wall is firmly rebridged, about three months after the last stage. The binder is simply a three or four inch soft sponge rubber ball which is strapped in the thoracoplasty depression under an encircling piece of stockinette by three three-inch strips of adhesive slightly longer than the circumference of the patient's chest. These are applied in the sitting posture. X-rays films are taken when the binder is off. This binder has superseded all others and has been a great help in controlling paradoxical respiration and keeping revision operations at a minimum.—*A Thoracoplasty Binder, E. F. Skinner, J. Thoracic Surg., April, 1945, 14: 171.*—(W. M. G. Jones)

**Skin Flap for Large Cavities.**—The author presents 2 cases with extensive bilateral tuberculosis and cavitation not suitable for any form of collapse therapy. A skin flap was used in each with excellent results and eventual rehabilitation. The procedure is not difficult and cases do not require close continuous aftercare.—*Drainage of Cavities in Bilateral Pulmonary Tuberculosis, V. S. Randolph, J. Thoracic Surg., October, 1945, 14: 395.*—(W. M. G. Jones)

**Lobectomy versus Thoracoplasty.**—The physio-pathological aspects of these two methods of treatment for upper lobe lesions

are discussed. Both have the same objectives in view, viz. to control or eradicate the diseased focus and permanently preserve the function of the remaining healthy lung. Thoracoplasty seems to be more successful, chiefly because it does preserve the function of the remaining healthy lung better than primary lobectomy, which necessarily entails overdistension of the lower lobes. Overdistension may be a precursor to emphysema. When a lung harbors a tuberculous lesion of low-grade activity, an unphysiological and undesirable condition exists which is not conducive to healing. The absence of X-ray evidence of disease in apparently healthy lung by no means rules it out. Tuberculosis is always bilateral, whether visible or not. Another factor of great importance is endobronchial tuberculosis which is present in all cases of tuberculosis with cavitation. When severe and producing obstruction, one finds either obstructive emphysema, suppuration, atelectasis or tension cavities. It is some form of this complication more than any other that defeats the aim of thoracoplasty and is advocated by the proponents of primary lobectomy as the chief indication for its use. However, at least 75 per cent of these cases with endobronchial disease respond to thoracoplasty, and in the few failures lobectomy can still be done with less risk and without overdistending the remaining lung. The evil effects of overdistension are best seen in the "good chronic" who heals his tuberculosis by atelectasis. One sees a reduction in the size of the chest, a decrease in costal movement or expandibility, contraction of the diseased area and compensatory distension of the remaining lobes or lung. At autopsy one sees both obstructive and overdistension-types of emphysema. Nevertheless it is recognized that there are many cases of apparent cure in which both upper lobes or a whole lung is destroyed by disease and the remaining lung shows severe overdistension without the picture painted above. These cases may be exceptions to the rule; and the overdistension is a very slow and gradual process in contrast to the rapid changes

subsequent to lobectomy. Another factor is that overdistension is not only unfavorable to healing, should tuberculous foci be present, but the bronchi in this area lose some of their normal motility, which is an important factor in favoring bronchogenic spreads. Thoracoplasty is successful because it utilizes four of the five basic principles of therapy: drainage (bronchial), immobility, relaxation and compression. The fifth principle, resection, is reserved for its failures. Bronchspirometric determinations on thoracoplasty patients show there is a significant reduction in function in only 25 per cent of the cases following a modern six-rib operation. Upper lobectomy should therefore be secondary to thoracoplasty failure and has not been difficult to perform when adequate exposure is obtained. —*Primary Upper Lobectomy versus Modern Selective Thoracoplasty in the Treatment of Tuberculosis, J. M. Chamberlain, J. Thoracic Surg., February, 1945, 14: 32.*—(W. M. G. Jones)

**Pulmonary Resection for Tuberculosis.**—Report of 17 lobectomies and 15 pneumonectomies for pulmonary tuberculosis done between October, 1940 and May, 1944. All of these were done by the hilar dissection technique. The most frequent indication for lobectomy has been an open cavity with positive sputum. In some cases the cavity had remained open in spite of an apparently adequate collapse by pneumothorax; in others pneumothorax was impossible because of pleural adhesions. Several completely collapsed lower lobes continued to be the source of positive sputum despite the fact that no cavity could be demonstrated by ordinary X-ray films or laminograms. A middle lobe was excised because of a stenosis of its bronchus. In only one case was the removal of an upper lobe undertaken deliberately (in a seventeen year old girl) when thoracoplasty would have been ordinarily the procedure of choice. In this group there were 13 excellent results (76.5 per cent), one with persistent positive sputum from bronchial stump ulceration and 3 deaths (17.6 per

cent). The commonest indication for total pneumonectomy has been stenosis of the bronchus. Of the 10 patients with stenosis, 7 made an uncomplicated recovery. Of the whole group, 8 are well or working (53.3 per cent); 3 died (one of embolism, one of infection and one of contralateral reactivation), but 2 others have empyema and lung disease; the last 2 have positive sputum (from the opposite bronchus and stump ulceration). What would appear from a radiological standpoint a perfectly simple procedure may prove exceedingly difficult because of extensive adhesions, chiefly between diseased and adjacent lobes and or incomplete development of interlobar fissures. Lobectomies for cavities in close proximity to the interlobar fissures are likely to be difficult or even impossible. Neither partial nor total pneumonectomy should be undertaken while the bronchoscopic appearance still suggests the presence of an active tuberculous bronchitis at or near the site at which the bronchus will have to be divided. If a collapse of the apex of a lung be considered necessary in a patient who may subsequently require a pneumonectomy, an extrapleural pneumothorax is the procedure of choice rather than a thoracoplasty. The author closed the bronchus with a running suture of chromic catgut on an atraumatic needle, sometimes reinforced by a few interrupted stitches of fine silk.—*Total and Partial Pneumonectomy in the Treatment of Pulmonary Tuberculosis, R. M. Janes, J. Thoracic Surg., February, 1945, 14: 3.*—(W. M. G. Jones)

**Pulmonary Resection for Tuberculosis.**—These cases represent all resections for tuberculosis done between 1934 and July, 1943. Those done before January 1, 1942 (18) are reported separately as the modern technique had not been worked out before. The 45 operations done since January 1, 1942 represent those done by hilar dissection and the pleural flap method of closing the bronchus. Division into "desperate risk" and "reasonable risk" groups is made. Thirty-five of the cases were pneumonectomies and 28 lobec-

tomies. Twenty-three patients (37 per cent) had endobronchial tuberculosis. Fifty-one of the 61 cases reported were women (2 cases had bilateral resection). Only 6 had negative sputum. The indications for resection are as follows: (1) for associated suppurative disease, 10 cases; (2) post-thoracoplasty, uncontrolled disease, 11 cases; (3) extensive multilobar, unilateral tuberculosis, 27 cases (most of these patients had very extensive and active tuberculosis, all treated by pneumonectomy); (4) upper lobe cases, resection elected in preference to thoracoplasty, 5 cases; (5) basal tuberculosis, 7 cases; (6) miscellaneous groups, one case each: recurrent hemoptysis following thoracoplasty, tension cavity, and a tuberculoma. The all-too-common complications of persistent fistula and tuberculous empyema were almost eliminated entirely from the second group of 45 cases; there was only one fistula and no case of tuberculous empyema. Contralateral spread appeared in 5 cases in this group (11.1 per cent). The only other serious complication was tuberculous ulceration in the stump of the bronchus (also 11.1 per cent), which occurred at the site of the mattress sutures. These sutures are now omitted and a simple end closure with silk is used. Routine post-operative bronchoscopy is strongly urged at interval of six weeks and six months. Five of the 45 cases died (11.1 per cent). The mortality for reasonable risks was 5.5 per cent, and for desperate risk cases 33.3 per cent. There were also 5 late deaths, but only 2 of these patients died of tuberculosis. Follow-up of the entire series (May, 1943) showed 15 of the 61 patients have died; of the remaining 46, 34 are clinically well and 26 are working. Of these 46, 13 have positive sputa on smear or concentrate. Resection is believed to be the treatment of choice: (1) in preference to thoracoplasty in cases with active parenchymal disease complicated by bronchial stenosis; (2) in extensive basal tuberculosis with or without associated bronchiectasis; (3) in unilobar disease that has failed to respond to pneumothorax with apparently adequate collapse; (4) in uni-

lateral disease that has failed to respond to an adequate thoracoplasty; (5) in preference to cavernostomy in the treatment of tension cavities in unilobar or extensive unilateral disease; (6) in extensive unilobar disease with dense opacities and little evidence of fibrosis and retraction; (7) in progressive unilobar or unilateral tuberculosis in the teen-age group; (8) for tuberculoma. Thoracoplasty before resection of the lung is considered contraindicated and unnecessary. The danger of contralateral spread can be reduced by careful suction of all secretions as they collect and by placing a temporary ligature around the bronchus early in the dissection whenever possible. Pulmonary resection can be performed safely in the presence of an extending active lesion, and complications have not been encountered in these cases more often than in the inactive group. Tuberculous bronchitis, either active or inactive, is not within itself a contraindication to resection, even if it has to be traversed during the procedure. To be a contraindication to resection, the contralateral lesion must be either uncontrolled or uncontrollable. Pneumothorax is permissible on the contralateral side in lobectomy, but not in pneumonectomy. Only 2 of the living patients have progressive contralateral disease, showing that the vast majority of cases handled the contralateral lesion without difficulty. The extent of resection cannot always be definitely determined prior to exploration as considerable disease may be found in a lobe where it was not suspected by X-ray studies.—*Pulmonary Resection in the Treatment of Tuberculosis*, R. H. Overholt & N. J. Wilson, *J. Thoracic Surg.*, February, 1945, 14: 55.—(W. M. G. Jones)

**Pulmonary Resection for Tuberculosis.**—The indications for lobectomy are: (1) tension cavities which failed to respond to pneumothorax or where pneumothorax was not advisable; (2) predominantly bronchial type of tuberculosis, perhaps with little cavitation; (3) lower lobe cavity not responding to pneumothorax; (4) extensive caseation of one

lobe with little cavitation and with disease almost limited to the one lobe; (5) a shrunken destroyed lobe with extensive cavitation with contralateral lung normal or contralateral lung requiring perhaps later collapse therapy; (6) unilobar disease in a young patient in preference to thoracoplasty, especially if still in the growing age period. Lobectomy conserves more pulmonary function than does thoracoplasty. The degree of tuberculous activity permissible in this group is a question, and some of these patients had elevated sedimentation rate, slight fever and an elevated pulse rate. Others had had extensive bilateral disease one or two years prior to operation. The only patient who died from contralateral spread in this series had a large amount of sputum. Cases presenting on the operation table an unsuspected involvement of the apex of the lower lobe or those in which the fissure is incomplete or fused were usually not given lobectomy and some other procedure substituted. (A lateral tomograph is of some help in depicting interlobar fissures before operation when other means fail.) Oxygen-ether is preferred as it gives a smooth anesthesia. Silk was used throughout; and the bronchial stump always covered by a flap of pleura. The phrenic nerve was crushed following removal of a non-contracted upper lobe. The remaining lobe is freed of all adhesions to permit full expansion. All cases were drained by water-seal method for forty-eight hours. Duration of operation averaged four and one-half hours. No instance of shock was encountered, due to avoidance of anoxia, meticulous technique and adequate intravenous therapy. Bronchoscopy was not performed routinely after operation, but great care was used to avoid retention of bronchial secretions. Results: of 15 living patients, 13 are in good condition, 12 have negative sputum and 6 of these by culture. One had a small apical staphylococcus empyema cured later by a thoracoplasty. One case developed a tuberculous empyema and bronchial fistula which will require a thoracoplasty.—*Lobectomy for Pulmonary Tuberculosis*, H. C. Maier &

R. Klopstock, *J. Thoracic Surg.*, February, 1945, 14: 20.—(W. M. G. Jones)

**Massive Blood Transfusions after Lung Resection and Pulmonary Edema.**—Experiments on dogs show that massive whole blood transfusions following extensive lung resections are well tolerated if certain precautions are observed: if the amount of lung resection, the rate of infusion and the amount of infusion are kept within limits simulating clinical practice. Every cubic centimeter of blood lost during operation should be replaced by whole blood and there should be no delay in the replacement. Shock due to hemorrhage is more easily prevented than treated. When patients are given very large amounts of blood in a short period of time very little saline or glucose should be given in the following twenty-four hour period. As the average blood loss in lung resection is about 1,500 cc., three to five blood transfusions as replacement are in order, and pulmonary edema probably will not occur except in the presence of severe cardiovascular or pulmonary disease. (Even if all this blood is given rapidly citrate poisoning is unlikely as 2,500 cc. would have to be given in fifteen minutes to approach the fatal dose of sodium citrate in animals. If necessary, fatal toxic reaction from the citrate can be avoided by intravenous injection of calcium salts.) If a patient sustains a severe hemorrhage and whole blood is not immediately available, saline, glucose and plasma must be used to combat shock; but whole blood for replacement is necessary, only one must in these circumstances necessarily limit the volume of whole blood given to avoid the danger of pulmonary edema.—*The Use of Whole Blood Transfusion in Resections of the Lung*, T. F. Thornton, W. E. Adams, J. E. Bryant & L. M. Carlton, *J. Thoracic Surg.*, April, 1945, 14: 176.—(W. M. G. Jones)

**A Self-Retaining Scapula Retractor.**—"By shortening one blade of the Tuffier retractor and inserting pegs along the outer surface of the second (sliding) blade, this retractor

can be used as a self-retaining scapula retractor. No assistant is required to hold it, and there is no danger of perforating the parietal pleura during thoracoplasty. The exposure secured is excellent and the retractor will work well for either side of the chest."—*Self-Retaining Scapula Retractor for Thoracoplasty*, K. P. Klassen, *J. Thoracic Surg.*, October, 1945, 14: 414.—(W. M. G. Jones)

**Tuberculosis of Nasopharynx.**—Tuberculosis of the nasopharynx occurred in 18 of 24 cases of pulmonary tuberculosis studied at autopsy. The pathological process was generally an ulcerative lesion on the posterior portion of the roof and the upper portion of the posterior wall. Less frequently lesions were found on the posterior margin of the ostia of the Eustachian tubes and nasopharyngeal surfaces of the uvula and soft palate. In 4 of the 18 cases lesions were found only microscopically. Graf noted gross lesions in 36 per cent of 118 cases of pulmonary tuberculosis, while microscopically the incidence was 82 per cent. No nasopharyngeal tuberculosis was found either by gross or microscopic examination in the authors' cases of miliary tuberculosis. They agree with Dietrich that hematogenous infection is rare. The important etiological factor is the inoculation of the nasopharyngeal mucous membrane by the bacilli from the sputum. This explains the localization. The deep inferior cervical lymph nodes were involved, but not the superior cervical retropharyngeal nodes. Gross ulcers were irregular, ovoid, with undermined margins and yellowish-gray bases. Histopathological changes were observed primarily in the remnants of the lymphatic tissue and consisted of subepithelial tubercles with varying degrees of caseation. Clinically, tuberculosis of the nasopharynx may remain as the active source of reinfection after the arrest of the pulmonary process. Therefore, where sputum conversion does not occur, the nasopharynx should be investigated as a possible focus.—*Tuberculosis of the Nasopharynx: Its Frequent Incidence and Clinical Significance*, A. R. Hollender &

P. Szanto, *Dis. of Chest*, May-June, 1945, 11: 227.—(K. R. Boucot)

**Tuberculosis of Brain.**—Twenty-two cases of cerebral tuberculosis have been studied. They can be divided in asymptomatic (silent) and symptomatic forms. Five different types may be distinguished: (1) the tumorous type: symptoms depend upon the location of the lesion and include increased spinal pressure; (2) the encephalitic type which is really a tuberculous meningoencephalitis; (3) multiple tuberculomata; (4) meningeal types which are very hard to differentiate from tuberculous meningitis; (5) mixed types. In 15 cases an autopsy was performed. In all of them pulmonary tuberculosis was encountered which was active in 11 and inactive in 4. In all cases below fourteen years of age an active pulmonary lesion was found. Amongst the 4 inactive cases 2 presented the tumorous form of cerebral tuberculosis. In the brain, the lesions showed inflammatory reaction and fibro-caseous destruction. This is the most frequent finding and seems to be the common reaction of the nervous tissue to the Koch bacilli. The size of these lesions varies from pin-head to walnut. It has not been possible to verify if the meningeal infection or the encephalitic infection was first to start. One case of early cerebral tuberculosis has puzzled the author. The patient had succumbed to caseous-pneumonic tuberculosis and had shown no clinical symptom of cerebral involvement. The autopsy showed a fibro-caseous nodule of the size of a rice kernel in the inferior portion of the anterior orbital gyrus. This nodule showed a necrotic focus with many histiocytes and lymphocytes. There was thrombosis of the capillaries within the nodule and also in the surrounding tissue and numerous Koch bacilli were found. The author believes that possibly some cases of acute exacerbation of cerebral tuberculosis which are superimposed on preëxisting tuberculoma, may benefit from a treatment with Jousset allergen which caused some sensation at the time of its first publication in 1932. Revision and thorough study of this treat-

ment is advocated.—*Aspectos anatomo-clínicos de la tuberculosis cerebral*, J. Bernales, *Rev. méd. peruana*, May, 1945, 18: 145.—(W. Swienty)

**Arthrodesis of Hip.**—Thirty-two patients with unilateral tuberculous involvement of the hip were operated upon in the hope of producing fusion of the unstable joint. The patients varied in age, duration of disease, amount of incapacity and amount of joint destruction. Four types of surgical techniques were used: (1) the standard Hibbs procedure with transplantation of the greater trochanter of the femur across the joint line after reversal of its direction; (2) massive transplant of the anterior portion of the crest of the ilium across the joint line; (3) use of chips of various sizes after curettage; (4) simple curettage of the joint. Union of the joint was achieved in 80 per cent of the Hibbs type graft, 70 per cent following massive inlay graft, 50 per cent following chip graft and no union in the one acute case in whom only curettage was performed. Although the percentage of successes resulting from the Hibbs and massive inlay grafts was nearly the same, the former procedure secured synostosis in an average of twelve months, whereas the latter averaged eighteen months. The distribution of cases in these two groups regarding the amount of destruction present according to preoperative X-ray evidence was essentially equal.—*Experiences with Arthrodesis for Tuberculosis of the Hip*, D. M. Bosworth & L. A. Green, *Quart. Bull. Sea View Hosp.*, January, 1946, 8: 39.—(P. Q. Edwards)

**Skin Tuberculosis.**—Presumptive evidence of a primary tuberculous complex of the skin consists of histological and bacteriological proof of the tuberculous nature of the lesions and evidence that it is a primary infection. This latter criterion is often difficult to substantiate. Two cases are presented, both of which fulfill the above stipulations: a small, isolated tuberculous lesion of the skin with enlargement of the regional lymph nodes

and formation of a cold abscess. The superficial lesions as well as the adenitis were proved to be tuberculous by both culture and biopsy. In the second case there was a concomitant primary tuberculous complex in the lungs. Complete surgical removal of the skin focus and adjacent infected nodes does not result in any untoward results, such as a persistent draining sinus, and may be of value as a prophylactic measure against possible future dissemination to other parts of the body.—*Primary Tuberculosis of the Skin: Case Reports*, M. Weichsel & P. F. Salgado, *Quart. Bull. Sea View Hosp.*, January, 1946, 8: 62.—(P. Q. Edwards)

**Artifacts in Preparations of Tubercle Bacilli.**—Artifacts may arise from the mechanical manipulation of tubercle bacilli while they are being spread on a slide and from the staining procedure. An attempt was made to establish the real or artifact nature of beads and granular forms in tubercle bacilli. Much granules can be demonstrated in tubercle bacilli of various ages and morphology as derived from four-day old, one-month old and eight-month old cultures. Comparisons were made between preparation stained with methylene blue (Loeffler's on unfixed cells), a 1 per cent water solution of basic fuchsin, or Giemsa stain after acid hydrolysis (method used by Robinow, 1941). The latter revealed a granular component reasonably referred to as a nuclear body, which could be easily confused with the bodies described by Much. Upon closer comparison, however, dissimilarities are readily noted. In young cells the nuclear bodies generally number two, sometimes three, whereas the Much granules are usually larger and appear in varying numbers, often as many as six or eight. The latter granules are rather evenly distributed along the cell, whereas the nuclear bodies are located most frequently at the ends and not at nearly equal intervals. Similar differences were observed in cells from older cultures. No formed bodies within the bacillus corresponding to the granules of Much were seen in stained or unstained living prepara-

tions. The appearance of the Much granules is neither dependent on nor indicative of the presence of ether-alcohol soluble components. Extracted cells show them as well as unextracted. Tubercle bacilli that have been fragmented or otherwise rendered non-acid-fast no longer have the capacity to show Much granules. This is a rather unique characteristic, since, as a rule, formed structures of fixed cells stain whether the cell is intact or not. The granules decrease in number and size instead of density as the concentration of the stain is reduced; this would not have been the case if they represented structural components of the cell. These granules are not peculiar to mycobacteria; they can be demonstrated in acid-fast cells of a distinctly different origin. Treatment of Much-stained granular bacilli with 5 per cent phenol results in a dispersal of the stain throughout the cell body and if these solidly stained cells are again washed in sequence with Lugol's iodine, nitric acid and the remaining solutions of the staining technique, some of the bacilli become granular again. They may be fewer in number and may be in new locations relative to the whole cell. Ultimately the cell seems to give up its stain so that no or only a small number of granules appear. It is extremely unlikely that the formed structures of a fixed cell could behave in such a fashion, especially in shifting position. The beaded tubercle bacillus is another conspicuous structural variant of the uniform acid-fast rods. It appears only in carbol-fuchsin stained preparations and here not consistently. The chemical composition of the fuchsin, the concentration of the dye, and the presence of dilute sodium chloride in the dye, all influence the number of beads formed. In addition it has been shown that 95 per cent alcohol will dissolve or disperse these bodies. To obtain at will a high concentration of beaded cells in any preparation it is simply necessary to add to the regular carbol fuchsin solution 0.5 g. of sodium chloride per 100 ml. In this study it has not been possible to identify beads with any of the granular variants or inclusions of

the tubercle bacillus that are more definitely established as real and functional forms or components of this microorganism. The granules of Much and beads are similar in character and neither one represents a morphological unit of the tubercle bacillus. It is not possible to explain the origin of beads and granules. That they can be readily created in the actively multiplying cells from young cultures suggests that they are not dependent upon degeneration products for their appearance. They may represent small dense concentrations of dye developed from some reaction between solvents and stain. The *Mycobacterium tuberculosis* does apparently not have a great variety of viable forms connected with its reproduction. Unquestioned is the acid-fast rod, which may show branching and which, after appropriate staining, shows what seem to be nuclear bodies. Of this form, newly developed cells may be weakly acid-fast and take the counterstain. It seems likely that Much's granules and beads are of similar origin and are both artifacts of the staining procedure.—*Some Artifacts Encountered in Stained Preparations of Tubercle Bacilli: II. Much, Granules and Beads*, K. R. Porter & D. Yegian, *J. Bact.*, November, 1945, 50: 563.—(F. G. Petrik)

**Fluorescent Method for Detecting Tubercle Bacilli.**—A method is presented for preparing and staining smears for the fluorescent method involving the use of a blending agent, methyl cellulose, with or without prior enzyme treatment of the sputum. The blending agent tends to separate the bacilli from the artifacts and make their recognition easy. The quality of the slides seems to be improved by treating the sputum with a water solution of pancreatic enzymes. The addition of dried bile to the enzyme solution may also be helpful in reducing artifacts. The enzyme may act to reduce artifacts because the latter are fatty substances that react with lipase, or the enzyme may alter the structure of the sputum so that better blending results. Good slides can be prepared without the enzyme

treatment and users may decide to simplify the method by its omission.—*Improvements in the Fluorescent Method for Detecting Tubercle Bacilli*, D. S. Stevens, J. Lab. & Clin. Med., October, 1945, 30: 892.—(F. G. Petrik)

**Peculiar Corpuscles in Tuberculous Material.**—The author describes, with the aid of illustrations, sparsely occurring bodies found from time to time in the examination of tuberculous sputum. These cone-like bodies are felt to be fungi of the yeast-oidia group. They occur in association with tubercle bacilli. In several instances, mycelia-like elongations were noted protruding from the mother cell. Large stratified cells similar to those reported from tissue of Schaumann's disease were noted. The association and significance of these findings are not known.—*On Peculiar Corpuscles Occurring in Tuberculous Material*, V. Hallberg, Acta med. Scandinav., April 8, 1943, 113: 412.—(E. R. Loftus)

**Egg Powder for Media.**—Dried egg powder is becoming available in Europe. It is, therefore, recommended for the preparation of media for the cultivation of tubercle bacilli: 120 ml. fresh milk, 5 g. potato flour, one small potato are heated in the boiling water bath, for one hour. After cooling to 60° C. the following mixture is added: 60 to 70 g. dried egg powder, 10 ml. glycerol, 5 ml. of a 2 per cent aqueous solution of malachite green, 1.5 to 2 g. asparagin and enough water to make up to 200 ml. The medium is tubed and sterilized in the usual manner.—*Kultivácia Mycob. tuberculosis na pôle z prášku zo sušených vajec*, I. Friedmann, Časopis Lékařů Českých, April 19, 1946, 85: 516.—(O. Felsenfeld)

**Weltmann Reaction.**—The Weltmann reaction is influenced by the pH of the medium. Because of the disagreement of several authors regarding the importance of the calcium level for the reaction, 10 patients received high doses of calcium intravenously and the blood

calcium level as well as the Weltmann reaction before and after the injections were tested. While a considerable increase of the blood calcium was observed, the Weltmann reaction was unaltered or showed a slight shift to the right. It is concluded that other points also play a rôle in the establishment of the reaction.—*Pokus o výklad Weltmannovy reakce*, M. Skyba, Lékařské Listy, February, 1946, 1: 45.—(O. Felsenfeld)

**Bacteriostasis of Oils for Tubercle Bacillus.**—(1) The bacteriostatic action of peanut oil, cod-liver oil and gomenol for the H37 strain and the bovine and avian types was determined. (a) Peanut oil is inhibitory for virulent human strains in a concentration of 5 per cent; for the bovine type in a concentration of 2 per cent; for the avian type the limit of tolerance was not determined, but it is greater than a concentration of 10 per cent. (b) Cod-liver oil is bacteriostatic for the human, bovine and avian types in 1 per cent concentration. (c) Gomenol is bacteriostatic for both human and avian types in 5 per cent concentrations. Complete inhibition of the bovine type occurred in 1 per cent concentration. (2) Prolonged incubation of virulent human strains with peanut oil, cod-liver oil and gomenol does not alter the virulence or the acid-fastness of the organisms, although the colony morphology is altered. (3) Complete lysis of colonies by oil was not observed. (4) After exposure of the human and bovine strains to the inhibiting effect of oils, a rich medium is required for growth. (5) It is suggested that the oils adherent to the tubercle bacilli inhibit the growth of this bacillus by a physical rather than a chemical action.—*Studies in Oleothorax: I. The Bacteriostatic Action of Oils on the Tubercle Bacillus*, P. D. Crimm & Veronica F. Martos, J. Thoracic Surg., August, 1945, 14: 265.—(W. M. G. Jones)

**Sulfadiazine in Experimental Tuberculosis.**—Twenty-four guinea pigs were inoculated with tubercle bacilli. Six animals were not treated; 6 received from the day of the inocula-



tion 300 mg. sulfadiazine daily (group A); in 6 animals the same treatment was started one week after inoculation (group B); in 6 animals it was begun three weeks after the inoculation (group C). The dose of sulfadiazine was later diminished because of its toxic effects. One animal of each group was sacrificed after fifteen days, one, one and a half, two and three months; no animal in any group lived longer. In group A a favorable action of the drug on the bacilemia and inhibition of propagation to the organs for some weeks was seen; the effect was less favorable in group B; group C showed rather an acceleration of caseation.—*Sulfadiazine et tuberculose expérimentale du cobaye, M. Giroux, Laval méd., January, 1946, 11: 24.*—(G. C. Leiner)

**Streptothricin and Streptomycin in Experimental Tuberculosis.**—The tuberculostatic activity of streptothricin and streptomycin upon the human tubercle bacillus was studied *in vitro* in Kirchner's medium. Streptomycin was found to be approximately 20 times more active against the tubercle bacillus than streptothricin. The toxicity of the two drugs for the developing chick embryo was tested in various concentrations. Streptothricin was approximately four times more toxic than streptomycin. The inhibitory effect of streptomycin on the development of tubercles in the chorioallantoic membrane of the chick embryo following incubation of bacilli with the drug at 37.5° C. for twenty-four and forty-eight hours has been established.—*The Tuberculostatic Action of Streptothricin and Streptomycin with Special Reference to the Action of Streptomycin on the Chorioallantoic Membrane of the Chick Embryo, E. W. Emmart, Pub. Health Rep., November 30, 1945, 60: 1415.*—(G. C. Leiner)

**Inhibition of Tubercle Bacillus by Aspergillie Acid.**—The inhibitory action of aspergillie acid on two strains of *M. tuberculosis*, H37 and a fast-growing human type, was investigated. The media used were Long's synthetic medium, with and without

ferric ammonium citrate and bacto-nutrient broth. On the latter medium, only the fast-growing tubercle bacilli multiplied readily. Liquid media were used for the fast-growing strain: agar was added for growing the H37 strain. Aspergillie acid was added to the media as the sodium salt. Aspergillie acid in low concentrations (1:80,000) inhibits the growth of *M. tuberculosis* in media to which no ferric ions were added. Ferric ions are precipitated by aspergillie acid. It seems likely that iron is essential for the growth of *M. tuberculosis*; aspergillie acid inhibits the growth by interfering with the utilization of iron of perhaps also by interfering with the functioning of iron-containing enzyme systems.—*The Antitubercular Activity of Aspergillie Acid and Its Probable Mode of Action, A. Goth, J. Lab. & Clin., Med. November, 1945, 30: 899.*—(F. G. Petrik)

**Reactivation of Tuberculin Reaction.**—Eight cases are reported of spontaneous activation at the site of a previously negative tuberculin test. This activation coincided with a primary infection which had occurred some time following the negative skin reaction. At the time at which the phenomenon of spontaneous activation occurred newly performed tuberculin tests were positive. The cases were observed among student nurses exposed to tuberculosis. The interval between performance of the tuberculin reaction and the appearance of spontaneous activation was 119, 84, 55, 24 and 15 days, respectively. The last 2 cases were considered as belonging to a somewhat different category since the tuberculin reaction possibly may have been performed within the pre-allergic phase and after the primary infection had already taken place. In 2 cases the primary infection remained clinically silent. In all other cases more or less severe symptoms were present during this period: chest pain, joint pain, loss of weight, episodes of fever. One case presented fever with development of erythema nodosum and fatal tuberculous meningitis shortly thereafter. In 4 cases X-ray examination revealed foci in the parahilar region.—*Nourcaux*

*cas de virage spontané de la cuti-réaction a la tuberculine*, E. Rist & Ch. Coury, *Rev. de la tuberc.*, 1944-1945, No. 7-9, 9: 109.—(V. Leites)

**Vitamin C in Tuberculosis.**—Sixty persons, of whom 10 were normal and 50 ill with tuberculosis, were examined as to blood vitamin-C level and urinary excretion of the vitamin. The method of van Eekelen, Emmerie and Wolff was used for the determination of ascorbic acid, a method which includes the oxidized reversible acid as well as the reduced. Saturation was determined by intravenous injection of 300 mg. vitamin C and analysis of the content in the urine for the following three hours. Saturation existed when more than one-half was excreted. In group one, which consisted of 21 normals, healed or inactive patients, the blood values varied between 0.7 and 2.9 mg. per cent, with the average at 2.0 mg. per cent. Group two, consisting of 26 patients with productive tuberculosis, had values of blood vitamin C ranging from 0.5 to 3.0 mg. per cent, with an average of 1.85 mg. per cent. Group three, with 13 patients with exudative tuberculosis, had values from 1.0 to 3.0 mg. per cent and an average of 2.05 mg. per cent. There was no relation between the severity of the disease and the blood level of ascorbic acid. There was, however, a direct relation between the disease severity and the unsaturation, as determined by the amount of ascorbic acid needed to be injected to bring the urinary excretion up to normal. There was no relation between the blood value and the urinary deficit, except that saturation was reached more easily with high blood vitamin-C levels. Part of the discrepancy may be explained by the prevention of further oxidation of dehydroascorbic acid in those most ill, resulting in high blood values of the reversible oxidized acid. In the urine only the reduced acid appears, giving a truer picture. Determination of urinary excretion of injected ascorbic acid is thus the best method of studying vitamin C metabolism.—*Untersuchungen über den Vitamin C-Gehalt des Blutes bei Lungen-*

*tuberkulösen*, J. E. Wolf, *Schweiz. med. Wchnschr.*, June 9, 1945, 75: 506.—(J. Gerstein)

**Lung Volume and Ventilation.**—A method was worked out which permitted the measurement of the following pulmonary data: (1) residual capacity (usually termed residual air), that is, the amount of air left in the lungs after a complete expiration; (2) equilibrium capacity (usually called mid-capacity), that is, the amount of air left in the lungs after a normal expiration; (3) total capacity, that is, vital capacity plus residual capacity. Normal values for the residual, equilibrium and total capacity and the ratios  $\frac{\text{Equilibrium capacity}}{\text{Total capacity}}$  and  $\frac{\text{Residual capacity}}{\text{Total capacity}}$  were determined for 35 healthy persons, 16 males and 19 females. The upper normal value for the relation of the residual capacity to the total capacity was for males 30.2 per cent, for females 33.9 per cent. In cases of slight tuberculosis the values were the same as in normals. In cases of extensive tuberculosis the total capacity diminished considerably, the equilibrium capacity did not show any definite change, the residual capacity showed a definite rise. The cause of the increased residual capacity and the relatively increased equilibrium capacity was probably pulmonary emphysema or any air spaces in the lungs that were functionally inferior such as cavities. Similar findings were obtained in bronchial stenosis. Under pneumothorax treatment a decrease of all the values was seen, but the relation between the various data remained the same. A change of these ratios was found when there was one of the conditions present which produced the same effect in the cases of pulmonary tuberculosis without pneumothorax treatment. Thoracoplasty reduced the absolute values of total capacity, equilibrium capacity and residual capacity; the residual capacity showed a relative rise. In patients who had had thoracoplasties six to sixteen years prior to the examination, the lung volume was increased, apparently due to distention of the contralateral lung, but the rela-

tions between the volume fractions were the same as in recently operated cases. In 14 cases the lung volume was determined before and one to two months after pneumonectomy or lobectomy. The remaining lung tissue increased in volume and a rise in the ratios  $\frac{\text{Residual capacity}}{\text{Total capacity}}$  and  $\frac{\text{Equilibrium capacity}}{\text{Total capacity}}$

took place. In cases examined some years after operation these increased values seemed to have diminished in connection with an increase of the total capacity. During the air insufflation in pneumothorax treatment expansion of the thoracic cage takes place. The physiological dead space is that part of the inspired air that is left behind in the air passages and thus does not reach the alveoli. A new method was devised to determine the dead space. With this method, uneven ventilation has an enlarging effect on the dead space. The value obtained for the dead space gives a fairly good idea of the effectiveness of ventilation. The dead space was in 8 normal males between 0.13 and 0.26 liters, in 4 normal females between 0.09 and 0.14 liters. In 10 out of 12 cases of emphysema a dead space of more than 0.26 liters was found. In cases of bronchostenosis there was an absolute and relative increase in the dead space. In cases of far advanced pulmonary tuberculosis without collapse therapy an enlarged dead space was usually found. In pneumothorax no important change of the ventilation efficiency in respect to dead space and uneven ventilation was found. Thoracoplasty did not, as a rule, lead to marked differences in the efficiency of ventilation. After some time a slight impairment of the ventilation might arise due to "complemental emphysema." After lobectomy and pneumonectomy the efficiency of ventilation was reduced, probably due to distention of the lungs. There is probably a reflex mechanism by which diminution of the lung volume produces an increase of the thoracic volume; this then is the cause of a permanent distension of the lungs. This reflex possibly serves to maintain a respiratory surface of a certain size and to facilitate the blood flow through the lungs. In general, a

relative increase of the equilibrium and residual capacities was associated with dyspnea. The presence of the same vital capacity in individuals of the same size does not imply that their lungs have the same functional capacity. This is, however, more probable if the residual capacities are equal.—*Lung Volume and Ventilation Efficiency: Changes in Collapse-treated and Non-collapse-treated Pulmonary Tuberculosis and in Pulmonectomy and Lobectomy*, G. Birath, *Acta med. Scandinav.*, Supplementum 154, 1944.—(G. C. Leiner)

**Positive Pressure Respiration.**—Experimental studies were carried out on dogs anesthetized with pentobarbital sodium to determine the effect of long periods of pressure breathing alone and when combined with a cute hemorrhage or trauma of the hind limbs. The following results were obtained: (1) Continuous positive pressure respiration with a pressure of 20 cm. of water. a) Five of 9 animals survived three hours of continuous positive pressure respiration, but the other 4 developed fatal apnea. b) The apnea caused by a continuous positive respiratory pressure of 20 cm. of water was not affected by large doses of atropine but was abolished by bilateral vagotomy. c) Continuous positive pressure respiration had a variable effect on the femoral arterial pressure and on the heart rate. It slowed and deepened the respirations. It elevated the jugular venous pressure, the renal venous pressure, the pulmonary arterial pressure and the pulmonary venous pressure. It decreased the diameter of the heart and thoracic inferior vena cava but increased the diameter of the abdominal vena cava. It dilated the tracheobronchial tree. d) Three of 8 animals survived two hours of continuous positive pressure respiration after a hemorrhage of 30 cc. per kilogram of body weight in five minutes, but the other 5 animals developed either apnea or circulatory failure. e) Three hours of continuous positive pressure respiration did not cause either pneumothorax or mediastinal emphysema in a single case, but in all of a group of 5 animals acute parenchymal and subpleural emphysema developed. (2)

Intermittent positive pressure respiration with a pressure of 20 cm. of water. a) All of a group of 5 animals withstood three hours of intermittent pressure respiration without difficulty. b) Intermittent positive pressure respiration produced considerable fluctuation of the femoral arterial pressure with a decrease of the mean pressure. It elevated the jugular venous pressure, the pulmonary venous pressure, the renal venous pressure, and the pulmonary arterial pressure. It decreased the diameter of the heart and thoracic inferior vena cava but increased the diameter of the abdominal vena cava and the tracheobronchial tree. It slowed and deepened the respirations but had no consistent effect on the heart rate. c) Three of 5 animals survived, without difficulty, two and a half hours of intermittent positive pressure respiration following a hemorrhage of 30 cc. per kilogram of body weight in five minutes. The other 2 developed circulatory failure and the animals were given 10 cc. of blood per kilogram of body weight with such improvement that they were then able to complete the experiment. d) Splenectomized animals were unable to withstand even a small hemorrhage (10 to 20 cc. per kilogram of body weight) during intermittent positive pressure respiration. e) Trauma to the hind limbs during intermittent positive pressure respiration proved fatal to all 4 animals. It was demonstrated that the pressure breathing was a definite factor in hastening their death. f) Three hours of intermittent positive pressure respiration with a pressure of 15 cm. of water did not cause either pneumothorax or mediastinal emphysema in a single case, but in all of a group of 3 animals acute parenchymal and subpleural emphysema developed. (From the authors' Summary)—*Certain Effects of Positive Pressure Respiration on the Circulatory and Respiratory Systems*, D. T. Carr & H. E. Essex, *Am. Heart J.*, January, 1946, 31: 53.—(G. C. Leiner)

**Intrapleural Gases.**—Textbooks generally agree that the diffusion of gases in the pleural cavity is dependent upon the partial pressure differential between the gases in the pleural

space and those in the venous circulation, thereby providing a *modus operandi* for the moving of the gases into the venous circulation. The pleura itself also plays a vital rôle in modifying the diffusion of gases. The mechanism of pleural absorption was demonstrated experimentally by a study of the gases in the pleural cavities of 44 patients with uncomplicated unilateral pneumothoraces: 50 cc. of air was withdrawn from the pleural cavity for direct analysis of oxygen and carbon dioxide content by the Haldane-Boothby-Sandiford method. Nitrogen content was the amount left after subtracting the other two. Volumes per cent of the respective gases were calculated by the Coryllos formula. In 145 analyses on 44 patients, the oxygen volume percentages in the pleural space were much below the level of oxygen in the venous system: average volume percentages were 2.8 or 19.96 mm. Hg. in the pleural cavity, whereas those in venous blood are reported as 5 or 38 mm. Hg. High concentrations of oxygen were then used to wash out the pleural space. The oxygen per cent was determined within seventy-two hours and found to be at the original level, far below the level in the venous blood. Hence, oxygen volume percentages in the pleural cavity are obviously not in equilibrium with the venous system, except during the first twenty-four hours after refills. Nitrogen is an inert gas, taking no part in metabolic processes and should theoretically be in equilibrium with the partial pressure of the tissues and venous system. The experimental data showed that the nitrogen partial pressure is above that in the tissues and venous system, probably because of the pressure of the expanding lung on the enclosed pleural gas, as well as the atmospheric pressure exerted on the pleural gases through the soft tissues of the chest wall. The consistently higher carbon dioxide content in the pleural space, which was found to be remarkably constant for a given individual, adds further indications that the pleural gases achieve equilibrium with the pleural tissues rather than the venous circulation. A constant relationship between oxygen and carbon dioxide volume percentages and

partial pressures, varying in inverse proportion, apparently represent a dependence of the amount of these gases upon the state of the oxidation process in the pleural tissues, that is, the visceral pleural tissue layers above the areolar layer. Only through such reasoning can the high volume percentages of carbon dioxide and oxygen, which are consistently found in the pleural cavity, be satisfactorily explained.—*A Study of the Behavior of Gases in the Pleural Cavity in Artificial Pneumothorax Therapy for Pulmonary Tuberculosis*, G. G. Ornstein, M. Herman & Marcella Friedman, *Quart. Bull. Sea View Hosp.*, January, 1946, 8: 5.—(P. Q. Edwards)

**Intrapleural Gases in Bilateral Pneumothorax.**—If the volumes per cent of oxygen carbon dioxide and nitrogen in the pleural cavity were dependent on the volumes percent and partial pressures of these gases in the venous system, then the readings in both pleural cavities should be identical to those in the venous circulation. Other fundamental questions, such as (1) the effect of the degree of lung collapse on the gas percentages, (2) the influence of gases in one pleural space upon those in the other and (3) the volume of gas absorbed from both pleural cavities of the same individual, were also answered by investigating the behavior of gases simultaneously in two pleural cavities. Analyses of the gases in the pleural spaces of 3 patients with uncomplicated bilateral pneumothoraces were made. The belief that the pleural gases are in equilibrium with the venous circulation was disproved by the following data: (1) the pressure of oxygen in the pleural cavities ranged from 2.71 to 23.3 (average 9.0), whereas the oxygen in venous blood is around 40.0 mm. Hg., (2) carbon dioxide pressure was similar to venous carbon dioxide in one patient, but significantly higher in the pleural spaces of the other 2 patients, (3) there was a marked dissimilarity between the two pleural spaces in each of the 3 patients studied. That the degree of lung collapse does not cause stagnation of the blood in the pleural vessels and thereby account for the low partial pressures and

volumes per cent of oxygen and the high levels of carbon dioxide in the pleural cavity (according to the textbooks), was adequately demonstrated by the results obtained in this study. No correlation was found between the partial pressures and the degree of lung collapse. The one logical explanation for this phenomenon is that the local metabolic processes in the pleural layers above the areolar layer in each pleural cavity determine the volumes per cent and partial pressures of the oxygen and carbon dioxide. Bilateral studies further revealed that there is no diffusion of gases from one pleural cavity to the other; each pleural cavity is entirely independent and unaffected by the volume per cent and the partial pressure of the gas in the opposite pleural cavity.—*The Behavior of Gases in Bilateral Pneumothoraces*, M. Herman, G. G. Ornstein & Marcella Friedman, *Quart. Bull. Sea View Hosp.*, January, 1946, 8: 28.—(P. Q. Edwards)

**Segments of Lung.**—The interlobar fissures divide the lungs into five lobes, three on the right, and two on the left. The distribution of the bronchi and arrangements of the blood vessels in the five lobes make it desirable to consider the lungs in terms of eight major structural units. The lower lobes are made up of two parts, a superior or apical portion designated as the dorsal division, and an inferior portion designated as the basal division. The right middle lobe and the lingula have similar divisions. The dorsal divisions have special significance both surgically and pathologically because they are the most frequent sites of pulmonary abscesses. Pulmonary cysts are also frequently localized here. On the other hand, bronchiectasis is found in the basal divisions and often is bilobar occurring in the middle lobe and the basal divisions of the lower lobes. This constitutes one of the most attractive possibilities for partial lobectomy. Bronchiectasis and cystic disease are often sharply localized in various segments of the basal division of the lower lobes. Occasional instances occur when partial upper lobectomy will obviate the necessity for total pneumonectomy, as in bronchiectatic cases where there is

involvement of the lower and middle lobes and the antero-inferior segment of the upper lobe. The importance of precise preoperative localization of pulmonary disease with accurate appraisal of boundaries in terms of bronchopulmonary segments cannot be over-emphasized. Roentgenograms, bronchography and bronchoscopy accomplish this. At the time of the operation, actual inspection and palpation of the lungs may aid in localization. If there is any question concerning the amount of tissue to be excised, the surgeon is obliged to err on the radical side. The excision of one or more of the minor pulmonary segments will have limited application and must be reserved for cases in which the lesion is peripheral and sharply localized. Neoplasms of the lung should not be treated by partial resection. The relative operative risks of partial and complete lobectomy are about the same. The author's experience is limited to 17 partial lobectomies with one death. During the same period, 55 complete lobectomies, about 50 per cent of which necessitated the removal of two lobes, resulted in one death. However, these figures are of no statistical value. The real importance of partial lobectomy lies in the possibility of conserving important amounts of lung tissue in selected cases.—*The Segments of the Lungs from the Standpoint of Surgical Procedures*, B. Blades, *Dis. of Chest*, May-June, 1945, 11: 203.—(K. R. Boucot)

#### Lobar and Segmental Collapse of Lung.—

The early diagnosis of disease requires the combined efforts of the medical and surgical facilities. The thoracic surgeon has made such advances in recent years that X-ray methods must be constantly reviewed and improved, for accurate localization, as well as knowledge of the nature of the pathological process, clarifies both the indications for surgery and the surgical technique. X-ray demonstration of collapse of the lung and its subdivisions depends upon well executed technique. Procedures are therefore reviewed which have been of most value. In the majority of patients routine anterior-posterior, Potter-

Bucky and lateral films furnish adequate information. The posterior-anterior film is the most valuable single part of the examination, but should be used primarily as a scout film. Pathological processes discovered should be fluoroscoped and a Potter-Bucky or Swedish grid and lateral film taken. In addition, oblique views, spot films and bronchography may be of value. Laminagraphy may give information not otherwise obtained. Fluoroscopy of all patients is an ideal not always attained and should be done to determine: (1) the dynamics of the chest, such as the extent and type of motion of the diaphragms, the position, size and type of pulsation of hilar shadows and mediastinal shift; and (2) the films necessary for best demonstration of the lesion. A relatively high kilovoltage is used at 4 ma. with the tube so located as to give 18 r per minute. During fluoroscopy spot films can be readily taken with the same kilovoltage at 50 ma. Findings should be recorded. A posterior-anterior film is needed in all cases for permanent record, but also to pick up minimal lesions that might be missed during fluoroscopy. Occasionally an X-ray film in full expiration may give more information than one at full inspiration. A lateral film should be taken in patients showing any abnormality in the posterior-anterior film or with a history of pulmonary disease. An anterior-posterior Bucky film permits further study of the bronchi and visualization of dense areas, fluid levels and bone detail. Eighty per cent of patients will need no further study to establish a diagnosis. If disease is bilateral, or if the study of the upper posterior part of the major fissures is desired, oblique views will often give more detail. Occasionally a posterior-anterior or anterior-posterior film taken in the lordotic position will reveal a lesion more clearly, such as collapse of the middle lobe. The necessity for such a film can be determined during the fluoroscopic examination. Laminagraphy has a definite place in the study of the bronchi, in separating normal from abnormal structures and for localizing a lesion. Most findings will have been evident before if X-ray methods are properly employed. As the patient re-

receives a large dose of radiation it should not be done indiscriminately. Bronchography also gives valuable information when it is indicated, but it may also obscure progression or regression of a lesion. In bronchiectasis, it serves as a guide to the surgeon in regard to the amount of lung which must be resected, but it is time consuming and in the majority of cases will offer little further diagnostic information than has already been obtained from fluoroscopy and X-ray. It is advisable to instill oil on the involved side first, obtain an anterior-posterior and lateral film and then, if there is a stenosing lesion, obtain a spot film at this time also. The opposite side should then be filled and anterior-posterior, Bucky and oblique films obtained. Artificial pneumothorax plus X-ray examination furnishes valuable information in some cases. Its use is indicated when it is difficult to determine the origin of a lesion, i. e., whether it arises in the parenchyma, mediastinum or chest wall. Advantage should be taken of certain factors affecting the quality of roentgenogram such as (1) the rotating anode tube, (2) a photo-timer or similar device, (3) intensifying screens of relatively small crystal size and cassettes with good contact. The modification of the optimum kilovoltage technique as described by Fuchs is of significant value in producing films of uniform quality and great diagnostic potentialities. The three principal types of X-ray films are technically easy and economical. Their diagnostic advantages are manifold.—*The Roentgen Appearance of Lobar and Segmental Collapse of the Lung (Technic of Examination)*, L. L. Robbins, C. H. Hales & O. E. Merrill, *Radiology*, May 1945, 44: 477.—(G. F. Mitchell)

#### Lobar and Segmental Collapse of Lung.—

This paper is intended to describe the roentgen appearance of certain structures which are likely to change in shape, size, position or contour when a lung, or any part of a lung, becomes collapsed. Some changes are only suggestive while others are pathognomonic of the presence of collapse. These observations are the result of the detailed study of 1,200

cases of tumor, bronchiectasis, foreign body, tuberculosis and 160 healthy young adult hospital employees. The similarity of the two sides of the chest offers in most cases a reliable means of discovering unilateral abnormalities. Thus, comparison of an abnormal lung with its normal opposite will often make an accurate diagnosis of collapse of a lobe or segment of a lobe possible. The study has demonstrated, that, in addition to the variations accepted as diagnostic of collapse, i. e., an abnormal shadow of increased density, elevation of the diaphragm, displacement or shift of the mediastinum and narrowing of the rib spaces, there are three additional anatomical factors. These factors are: (1) the appearance and arrangement of the vascular shadows in the peripheral portions of the lung fields, (2) the appearance and position of the hilar shadows and (3) the demonstration of the actual size of the lobe as determined by the appearance and position of the septa or fissures of the lung. Anatomically the hila are approximately at the same level, though in the X-ray film the left hilum appears to be a little higher due to the fact that the left-pulmonary artery is more clearly seen than the eparterial right main bronchus. Any marked deviation in the position of the hilum and in the pattern of the adjacent vascular structures strongly suggest spatial rearrangement within the lung. Thus collapse of an upper lobe moves the hilum upward, and in collapse of the lower lobe, the hilum moves downward. This may at first give the impression that the hilum of the involved lung is smaller. A comparison of the vascular structures in the periphery of the lung fields may show spatial rearrangement. Thus, greater separation of normal vascular network suggests that one portion of a lung or lobe occupies a much greater spread than normally. In the majority of cases it is possible to demonstrate the actual boundaries of the individual lobes by means of the postero-anterior and lateral roentgenogram. Lateral film and fluoroscopy will accurately localize a lesion seen in the postero-anterior film. In many persons about one-third of the lower lobe is below the horizontal plane of the dome



of the diaphragm and is not demonstrable on either single or stereoscopic X-ray films. Major septa are demonstrated only on the lateral roentgenogram. In this projection they run roughly from the level of the fifth thoracic vertebra posteriorly to the most anterior portion of the diaphragm. The greater septa may usually be distinguished from each other since on the right side it is met by the minor septum, and the leaf of the diaphragm the septum meets can usually be identified. Both postero-anterior and lateral films are of value in demonstrating the minor septum. This appears as a gently curved line extending from the anterior chest wall at about the level of the anterior portion of the third to fifth ribs to meet the greater septum in the mid-chest. The posterior portion does not change position, but the anterior portion moves upward during inspiration. A change in the position or course of a major septum will become more readily apparent if it is compared in the lateral projection with the septum on the opposite side of the chest. Any marked variation of the position or contour of any septum is strongly suggestive of spatial rearrangement and should be correlated with the study of the appearance of the peripheral vascular shadows and the position of the hilum on each side of the chest.—*The Roentgen Appearance of Lobar and Segmental Collapse of the Lung: II. The Normal Chest as It Pertains to Collapse, L. I. Robbins & C. H. Hale, Radiology, June, 1945, 44: 543.*—(G. F. Mitchell)

**Tomography.**—Tomography is regarded to be of value in the diagnosis of tuberculous cavities which cannot be seen in the plain film. However, even when cavity is not suspected, tomograms can still be of material aid in evaluation of tuberculous processes. The full extent of infiltrations is often not appreciated in the plain film, especially in the apical field. The over-lapping of clavicle and ribs, and the differentiation of pulmonary infiltrations from a thickened apical pleura are an important indication for tomograms. Serial tomograms can often be of special aid in evaluation of healing or progression of single infiltrates.

Lastly, it is often possible to get a clear picture of distortions and stenosis of the bronchial tree with the aid of tomograms.—*Die Bedeutung der Tomographie bei der nicht-kavernösen Lungentuberkulose, F. Rotach, Schweiz. med. Wchnschr., November 24, 1945, 75: 1029.*—(H. Marcus)

**Bronchography.**—Good anesthesia of the pharynx, larynx and trachea is the *sine qua non* of adequate bronchography. Phenobarbital is given one hour before the procedure. With the patient seated in a straight-backed chair and his head tilted far backward, he is instructed to hold his tongue out with a piece of gauze and to breathe audibly to help prevent swallowing the anesthetic agent which is given, 5 cc. at a time, drop by drop, into one nostril. The solution consists of: cocaine hydrochloride 2.0 g., phenol 0.2 g., epinephrine (1:1000) 10.0 cc., distilled water *q.s.ad* 150.0 cc. This solution is warmed to body temperature before using. Slowness of injection is important: 5 cc. should take five minutes. Coughing, which frequently occurs when the fluid reaches the glottis, is encouraged at this time as it helps to clear the bronchi of secretions. Two additional injections of 5 cc. each are made at least five minutes apart. The patient is then seated on a rolling table against an upright fluoroscope and cautioned not to cough or swallow until the procedure is completed. The suspected lung is examined first by having the patient lean backward and toward the affected side with the elbow and forearm supported on a pillow. Under fluoroscopic control 8 to 10 cc. of the iodized oil (at room temperature) are injected into the nostril drop by drop, exactly as was the anesthetic agent. When the posterior branches of the lower lobe bronchus are visualized, the patient bends forward, still leaning toward the affected side, to fill the anterior branches of the main lower lobe bronchus, as well as the middle lobe bronchus on the right or the lingula of the left upper lobe. Anterior and lateral X-ray films are taken at this time. Another 5 cc. of oil are injected with the patient still leaning towards the affected side. He then lies for



two minutes on his affected side with his shoulder hanging over the edge of the table. In this position the upper lobe bronchus and its branches may be filled. X-ray films are again taken in the anterior and lateral prone positions. The other side of the chest is then similarly examined, if desired, the only difference is the taking of oblique, upright and prone films instead of lateral views to avoid superimposition of the bronchial trees of both lungs. Three illustrated cases are presented in the paper.—*Bronchography: Details of a Simple Method*, P. S. Slater, *Quart. Bull. Sea View Hosp.*, January, 1946, 8: 47.—(P. Q. Edwards)

**Histoplasmosis in Children.**—The literature is reviewed from 1906 when Darling first described a case of "protozoan infection producing pseudo-tuberculosis in the lungs and focal necrosis in the liver, spleen and lymph nodes." He suggested the name *Histoplasma capsulatum* for the organism and "Histoplasmosis" for the disease. At first a rarity, since 1936 reports have appeared from all over the world, especially from the United States. In 1934 DeMonbre first cultivated the organism and classified it as a fungus. There have been 81 reported cases to date, 21 of which occurred in children, of whom 15 were less than 15 months of age. A case report is given together with a summary of the other 20 cases reported as having occurred in children. Most of these cases were from the North Central region of the U. S. The age range was from 7 weeks to 12 years. The duration of the disease was from one week to seven months with an average of three months. In adults the disease may appear as localized nodules or ulcers in the skin or mucous membrane or, more often, it is a systemic infection with special involvement of some organs—lungs, gastrointestinal tract, heart or joints. In infants the symptoms are different—fever, pallor, diarrhea, loss of weight or failure to gain, difficulty in feeding, chronic cough, irritability, abdominal distension, cyanosis with feeding, hepatomegaly, splenomegaly, lymphadenopathy, purpura, anemia, leukopenia. The diagnosis is made

by biopsy of the lymph nodes, spleen, bone marrow or cutaneous lesions or by blood smears which are occasionally positive. Blood culture on blood agar or on Sabouraud's medium requires several weeks. Lastly, the cutaneous test may be helpful. The prognosis is uniformly poor. Only one patient has been reported symptomatically well, four years after treatment with an antimony compound. Other cases have failed to respond to antimouy, sulfonamides, etc. Nothing is known as to the mode of entrance of the organism into the body. Intrauterine infection seems possible where symptoms develop before 3 months of age.—*Histoplasmosis in Children*, A. M. Iams, M. M. Tenen & H. F. Flanagan, *Am. J. Dis. Child.*, October, 1945, 70: 229.—(K. R. Boucot)

**Fluid in Pleural Space.**—In a study of 274 proved cases, 61 per cent (169 cases) were due to malignancy, two-thirds of these to intrathoracic or breast carcinoma. In one-third (44 cases) the aspirated fluid showed malignant cells. When the fluid is bloody there is a 95 per cent chance that a malignant process is present, provided congestive heart failure can be ruled out. In these cases, a bloody effusion may indicate pulmonary embolus with infarction (5 of 8 cases). Of the whole group, heart failure was found in 15 per cent (42 cases); pneumonia in 9 per cent (24 cases); tuberculosis in only 6 per cent (16 cases); cirrhosis of the liver in 3 per cent (8 cases, in 2 of which the effusion was bloody); chronic nephritis in 3 per cent (7 cases); miscellaneous conditions in 3 per cent. In 170 other cases the underlying disease was not proved. Of these, 58 had a tentative diagnosis of tuberculosis and 46 cases of suspected malignancy. Chylous fluid, frequently due to neoplastic diseases, is diagnosed only if the pleural fluid is carefully examined. When chyllothorax is suspected, the fluid should be stained with Sudan III and chemically analysed for fat.—*Significance of Fluid in the Pleural Space*, W. S. Tinney & A. M. Olsen, *J. Thoracic Surg.*, June, 1945, 14: 218.—(W. M. G. Jones)

**Hypercalcemia in Sarcoidosis.**—Abnormal values of the blood calcium in Boeck's disease have only rarely been recorded. In the past, two authors have reported a total of 11 cases of sarcoidosis in which the blood calcium has been elevated up to 15 mg. per cent. To these cases the authors add 3 cases of their own. No definite explanation for the hypercalcemia can be given at the moment. The most likely hypothesis is that sarcoidosis, with its tendency to involve bone, can be much more diffuse than is appreciated from the examination of roentgenograms of the skeleton. That bone involvement frequently occurs in the form of cystic degeneration is well known. However, bone may be extensively involved by disseminations of Boeck's lesions which are too small to appear on the X-ray film, but sufficiently numerous to influence the blood calcium. Diffuse bone lesions may raise the blood calcium primarily or secondarily through their influence on the parathyroid glands, such as is also seen in myeloma, osteomalacia, rickets, etc. One of the author's cases had very diffuse calcifications throughout the parenchymatous organs. In addition to miliary calcification in the lungs, there was calcification of a degree sufficient to produce X-ray alterations in the kidneys, spleen, gastric mucosa, periarticular spaces, small and medium sized arteries, together with a peculiar abnormal calcium deposition in the bone. This patient also showed pronounced signs of renal insufficiency, so that one may assume the additional renal factor in the disturbance of calcium metabolism. The calcifications in the parenchymatous organs may partly be due to calcifications of preëxisting Boeck's lesions, as for instance in the lungs, or they may be due to true metastatic calcifications in normal tissue. The authors advise the examination of the urine for abnormal calcium excretion in all cases of sarcoidosis.—*Hyperkalzämie und Organverkalkung bei Boeck'scher Krankheit*, A. Schüpbach & M. Wernly, *Acta med. Scandinav.*, November 8, 1948, 115: 401.—(H. Marcus)

**Hemothorax and Hemopneumothorax.**—Diagnosis of hemothorax as a result of war in-

jury was made mainly on the basis of flatness on percussion and absent tactile fremitus. In basal collapse the signs are limited to the paravertebral region, the breathing is bronchial, dullness less marked and moist sounds more common. In consolidation moist sounds occur, breathing is tubular, fremitus is normal or increased and signs are limited neither to axilla nor paravertebral area. Pneumothorax is diagnosed when the percussion note is hyperresonant. Treatment consists in aspiration done as early as possible. As much blood or air was removed as was possible without causing severe symptoms in the patient. Aspiration was done every other day. Air was aspirated as completely as possible at the start so that adhesions might take place between the apex of the lung and the parietal pleura.—*Traumatic Haemothorax and Haemopneumothorax*, T. Simpson, *Lancet*, October 27, 1945, 249: 521.—(J. Gerstein)

**Spontaneous Pneumothorax.**—One hundred and twenty-six patients with 129 episodes of spontaneous pneumothorax were observed among military personnel in the Army Air Forces Training Command. One patient had one recurrence and one patient had two recurrences. The age of the patients was between 18 and 41 years. There were no immediate fatalities. The onset was gradual in 17.8 per cent of the cases. Initial symptoms were absent or mild in 63.5 per cent. In 76 patients there was nothing in the past history that had any reasonable association with the onset of spontaneous pneumothorax. None of the onsets occurred during flight. In 48.6 per cent the onset was associated with a minimum of physical activity. In 13.6 per cent it was associated with extreme physical activity. The valvular type of pneumothorax occurred only twice. Spontaneous pneumothorax was seen on the right side in 59.8 per cent. A collapse of less than 50 per cent on the roentgenogram was observed in 59.5 per cent. The cause could usually not be found. Emphysema, pulmonary tuberculosis, pneumonia, pleurisy were each the cause of one spontaneous pneumothorax. The average number of days required for the air to be absorbed was

31.1. Three out of 4 patients were salvaged for further military duty. Seven patients gave a history of previous episodes of spontaneous pneumothorax. It is believed that rupture of an emphysematous bleb is probably the most common cause of spontaneous pneumothorax.—*Pneumothorax in Young Adult Males: Descriptive Statistics in One Hundred and Twenty-six Cases*, J. E. Leach, *Arch. Int. Med.*, November-December, 1945, 76: 264.—(G. C. Leiner)

**Spontaneous Pneumothorax.**—The authors were impressed by the number of inductees giving a history of spontaneous pneumothorax. That it seldom results in tuberculosis is well known, but many who have experienced it have been unduly alarmed, over-cautioned and developed chest symptoms bordering on hysteria when these cases should be treated like the accidents they really are. One hundred unselected cases were observed months to years after collapse. There was no notable predilection for either lung. It appeared to occur most often in the third decade of life and in none was there any occurrence before 16 years of age. About 2 per cent experienced recurrences, most being on the same side, and seldom occurring after 30 years of age. If two years had elapsed since the spontaneous pneumothorax occurred, the chance of recurrence is only about 10 per cent. As far as could be ascertained, none of the men were suffering from any chronic respiratory disease at the time and, except for 6 who experienced the condition following cough associated with acute respiratory disease, all were in good health. In 63 the spontaneous pneumothorax occurred during slight physical activity; 5 were asymptomatic and surprised to learn of its presence. In only 30 did it develop during intense physical exertion. It was found most frequently in the white race, rarely being seen in the colored in spite of the large number of the latter inductees. The authors are inclined to believe that the colored are less sensitive to the symptoms and therefore it goes undiscovered. Sixty-five were seen two or more years after reexpansion and all except 4 chest films ap-

peared perfectly normal. In none could it be predicted from the film if there would be a recurrence. There was a residual pleural thickening in one case who had had a hemopneumothorax, and one man had a productive lesion in the contralateral lung. A "queer feeling" in the chest and respiratory distress were the outstanding symptoms at the time. In some a diagnosis of pleurisy had been made, the chest strapped and the true diagnosis discovered following X-ray examination. In not a few instances among older men a diagnosis of angina pectoris or coronary occlusion was made. The treatment usually consisted of several weeks of bed-rest, the patient being allowed to return to work anywhere from three weeks to six months or a year after the lung was reexpanded. Advice offered by their physicians as to the man's activity varied from urging a cautious almost vegetable existence to advising the patient to forget about it. Some had been cautioned that tuberculosis might develop. Many men were, therefore, unduly apprehensive as to the possibility of future complications.—*Idiopathic Spontaneous Pneumothorax: History of 100 Unselected Cases*, L. Schneider & I. I. Reissman, *Radiology*, May, 1945, 44: 485.—(G. F. Mitchell)

**Bronchoscopy.**—The advantages of bronchoscopy, from a diagnostic and therapeutic standpoint, are described with relation to nontuberculous pulmonary disease. In 2 cases the diagnosis of bronchial neoplasm was made and appropriate treatment could be instituted. In one case a foreign body in the lung was successfully treated. In one case the diagnosis of inflammatory bronchial polyp with obstruction was made and excision performed. In 2 cases bronchoscopic drainage resulted in marked amelioration of symptoms. One was in an infected bronchiectatic cyst, the other in an infected cyst in pulmonary cystic disease.—*De la bronchoscopie dans les affections pulmonaires chroniques non tuberculeuses*, J. P. Secretan, *Schweiz. med. Wchnschr.*, November 18, 1944, 74: 1193.—(J. Gerstein)

**Immunization against Pneumonia.**—Many studies on prophylactic immunization against

pneumococcal pneumonia have been made, using a number of different antigenic preparations. The results, in the main, have been beneficial. In most of the studies, however, certain variables have clouded the interpretation of these results. Among the variables, the following appear to be of the greatest moment: differences in the composition of the immunized and control groups; uncertainty as to whether the specific pneumococcal types included in the vaccine were the same as those currently causing pneumonia; failure to determine whether the observed decline in cases in the immunized group was due to a decrease in cases caused by the pneumococcal types included in the vaccine; inadequate control of the antigenicity of the preparations used. In the present study, it is believed that the important sources of error have been eliminated, hence results can be interpreted with more assurance than has been previously possible. This study deals with the immunization of man with the polysaccharides of certain types of pneumococci. It has been demonstrated that the specific capsular polysaccharides are highly antigenic and they have other advantages. They rarely produce local abscesses associated not infrequently with whole pneumococcal vaccines, and a stable, water-clear solution of known composition can be prepared with them. The population chosen for vaccination, that of an Army Air Force Technical School, was large and the average duration of stay was six months. All the men spent the bulk of the day in close, indoor contact with one another. The School generally reacted to respiratory diseases as a whole and not by its individual component groups or units. From the point of view of experimental epidemiology this uniform behavior of the School population was a valuable trait. During the two preceding winters, (1942-44) high epidemic rates for pneumococcal pneumonia had prevailed in the school. Types II, I, V, VII, XII, and IV, in that order, caused 75 per cent of the cases of disease, the rates for the individual types being approximately the same for each year.

The living conditions and duties during the season of the experiment (winter, 1944-45) were unchanged, and the expectation was that the incidence of pneumonia would still be high and that the same types would persist. Accordingly, the solution used for immunization contained the specific capsular polysaccharides of pneumococcus types I, II, V and VII. Type XII and type IV remained as controls. Beginning September 20th, 1944, immunization by a single subcutaneous injection in the dose of 1 ml., containing from 0.03 to 0.06 mg. of each polysaccharide, was carried out on alternate members of the population. This insured a thorough mixing of immunized and non-immunized subjects in all phases of their activities. In all, 8,586 men received the vaccine and 8,449 were injected with saline (controls). The man-days of exposure were approximately the same for each group. Laboratory facilities were available for the typing of all cases of pneumonia. In addition, a continuous carrier survey for pneumococci was carried on throughout the period of observation, the total sample being 3,757 pharyngeal cultures with an overall pneumococcal rate of 57.7 per cent. The injection of the capsular substances as described was found to be effective in preventing pneumonia caused by the types in question but not that due to heterologous types. During the seven months of observation following the beginning of the immunization program, 4 cases of pneumonia caused by types I, II, V or VII occurred in the vaccinated group, as opposed to 26 cases among the non-vaccinated. There were 14 cases of type II pneumonia among the controls and only one in the vaccinated group. Yet there is no reason for believing that polysaccharides, of types I, V, and VII should differ in their immunizing capacity from that of type II. It is interesting to note that the 4 men who developed pneumonia of a type against which they had been immunized all did so within the first two weeks following the immunization injection. Tests for circulating antibodies were done on 8 vaccinated men and immunity was found to develop

from between six and nine days after injection, but usually required from three to six weeks to reach its maximum. This may explain why the only cases of homologous type pneumonia in the vaccinated group developed during the first two weeks after immunization. The incidence of the other types of pneumonia was about the same, 56 cases in the immunized group and 59 in the non-immunized. Thirty-two men in the immunized group and 59 in the non-immunized carried pneumococcus types I, II, V, or VII, or 1.79 and 3.26 per cent, respectively. The distribution of all other types was about the same in both groups, type XII being the most prevalent organism and also the cause of more cases of clinical pneumonia than any other single type during the 1944-45 season. Fifty-eight per cent of the total population were found to be carrying pneumococci of one or more types. The evidence suggests that immunizing one-half of the school population not only was effective in reducing the carrier rate for types I, II, V and VII in the immunized group, as shown above, but apparently prevented the development of high carrier rates in the non-immunized population. Of equal importance with the prevention of types I, II, V and VII pneumonia in immunized subjects was the reduction of infection to these types in the non-immune population as compared to the experience of the two previous winters. The observed incidence of pneumonia was one third or one fourth of the expected incidence. The conclusion is inescapable that immunization of half the population greatly reduced the incidence of the disease in the non-immune half. It explains why the number of cases available for testing the effect of the immunization was so far below the expected. The lessened number of contact cases and the lowered carrier rate in the immune group could well be responsible for this. Because of the relatively low incidence of pneumococcal pneumonia in civilian populations, anti-pneumococcal immunization is unlikely to become a general procedure. In certain groups at a greater risk, for example foundry

workers, miners and inmates of mental institutions, however, immunization would appear to be desirable. In military populations the greatest incidence of pneumonia occurs in new recruits, so that most benefit would be derived from immunization of this group.—*Prevention of Pneumococcal Pneumonia by Immunization with Specific Capsular Polysaccharides*, C. M. MacLeod, R. G. Hodges, M. Heidelberger & W. G. Bernhard, *J. Exper. Med.*, December, 1945, 82: 445.—(J. S. Woolley)

**Penicillin in Experimental Pneumonia.**—Pneumonia was produced in rats by introducing pneumococci by intratracheal intubation. A strain of type-I pneumococci was used. The animals received 0.15 cc. of a 1:100,000 dilution, the final dilution being in mucin. The median survival time of animals infected in this way was found to be 2.9 days. Infected animals were divided into four groups. The first group served as untreated controls and the others were given penicillin, at various times after infection, by subcutaneous or intramuscular injection, or by inhalation of an aerosolized solution. The sodium salt of penicillin was dissolved in the proper amount of M/50 phosphate buffer, pH 7.3, to give the desired concentration. The subcutaneous injections were made under the skin of the back and the intramuscular injections in the muscles of the hind leg. For aerosolization the animals were exposed to nebulized (DeVilbiss 40 nebulizer operated by compressed air) solutions transmitted through an eight-chambered glass manifold. The rats were confined in small wire cages and the bodies of the animals did not come in contact with the mist. By estimating the amount of phosphate in the aerosol the dilution of the penicillin could be readily determined, and from this the amount of penicillin that each animal received. In order to evaluate the three methods of therapy, it was undesirable to have a 100 per cent survival rate. Hence the dosage and its frequency were controlled by this factor. In all instances the penicillin was administered

at different periods after treatment, the time varying from three to twenty-four hours. The doses (from 250 to 500 units per rat) were of the same order of magnitude for the three methods of administration as evidenced by the concentration of penicillin in the urine. Most of the rats with experimental pneumonia yielded to therapy with penicillin. As good results followed penicillin given as an inhalant as after its injection.—*The Control of Experimental Pneumonia with Penicillin: I. Comparison of Inhalation and Injection Therapy*, Catherine E. Wilson, Carolyn W. Hammond, Anne F. Byrne & Eleanor A. Bliss, *Bull. Johns Hopkins Hosp.*, December, 1945, 77: 411.—(J. S. Woolley)

**Penicillin in Chest Wounds.**—A series of over 500 penetrating wounds of the chest were studied. Parenteral penicillin therapy was used only occasionally. The indications are: (1) when pulmonary suppuration or severe infection exists with a pyothorax that is being surgically drained; (2) in severe chest-wall lesions, associated with an open sucking septic pneumothorax. For a simple or infected hemothorax penicillin given parenterally is of little or no value. Penicillin is used locally in hemothorax as a prophylactic measure. At the forward units the intrapleural injection of 60,000 units in 6 to 10 cc. at the end of the first two or three aspirations is advised. In the general hospitals the uninfected hemothorax is treated by aspiration without intrapleural instillations except: (1) where there is coexistent chest-wall sepsis; (2) when there is recognized or suspected pulmonary infection; and (3) at the conclusion of a thoracotomy for foreign-body removal, penicillin, 120,000 units in 10 cc. of saline, is instilled after air has been drawn off. Penicillin is of greatest value in the treatment of infected hemothorax and empyemata. Intrapleural therapy is useless for effusions caused by Gram-negative organisms and penicillin-resistant staphylococci. The procedure used is to aspirate the effusion and inject 120,000 units of sodium

penicillin for large cavities and 60,000 units for smaller ones in 10 to 20 cc. of solution, on alternate days. This is continued until three specimens of the fluid have been reported to contain no pyogenic organisms on smear or culture. In chest-wall wounds, the septic chest-wall is excised and the closure is by suture; penicillin solution is introduced through a tube. This treatment is very successful even in the presence of frank pus.—*Penicillin in Wounds of the Chest*, A. L. D'Abreu & J. W. Litchfield, *Brit. M. J.*, April 21, 1945, 1: 558.—(D. H. Cohen)

**Enterococcus Pneumonia.**—Serious infections due to Lancefield Group 4 enterococci have been reported in the genito-urinary system, in the biliary tract, in peritonitis, endocarditis, sepsis, appendicitis and meningitis. The first report of pneumonia due to an enterococcus appeared in 1933. Since then many cases are on record. Clinically the disease is characterized by a severe, but usually benign course. High fever and leucocytosis are the rule. The disease is frequently bilateral and on the X-ray film appears as a patchy bronchopneumonia. The sputum in 7 cases reported in this paper contained enterococci, once in pure culture, and six times in association with staphylococci or streptococci. Pneumococci were absent in all 7. Clinically the disease is characterized by its resistance to sulfonamide therapy. This feature is so characteristic that enterococci should be specifically looked for in the sputum of all patients who were adequately but unsuccessfully treated with sulfa drugs. It is possible that enterococci are the cause of many atypical pneumonias which are characterized by a protracted course, fever and a hemorrhagic copious sputum.—*Über Enterokokkenpneumonie*, H. Lüdin, *Schweiz. med. Wchnschr.*, December 1, 1945, 75: 1058.—(H. Marcus)

**Sulfonamides in Pulmonary Abscess.**—Thirty-one cases of lung abscess were treated with different sulfonamide preparations. The

total doses were equal to 80, 90, 150, 200 and even 315 g. of sulfanilamide. While a temporary decline of the fever curve and diminution of the sputum were sometimes observed, no permanent effect could be seen.—*Yüksek doz sulfamidlerle iyi olmiyan 31 akciğer çibani vak'aları, Muzafer Şevki Yener, Türk Tıp Cemiyeti Mecmuası, December, 1945, 11: 533.*—(O. Felsenfeld)

**Lung Abscess following Shock Therapy.**—Two cases are reported in whom a lung abscess developed following treatment with electric shock for manic-depressive psychosis. In both cases the abscess developed in the left lung near the hilum. Treatment with penicillin resulted in cure in one case, in improvement in the other case. Shock treatment apparently produces conditions favorable for the development of a lung abscess. During the convulsion there is probably a circulatory stasis in the lower parts of the lungs, possibly with local thrombosis. The patient is apneic for a while, then breathes deeply and may aspirate pathogenic organisms from the upper respiratory tract.—*Accident rare au cours du traitement par l'électro-choc pulmonaire, A. Pelletier, G. H. Larue & M. Samson, Laval méd., December, 1945, 10: 726.*—(G. C. Leiner)

**Vitamin C in Wound Healing.**—Three factors of vital importance in poor wound healing are low blood protein, allergic reactions against the suture material and low blood ascorbic acid. Experiments by many workers show that the tensile strength of the scar depends upon the amount of ascorbic acid in the tissues. In scurvy, fibroblasts will grow in the scar but the quantity of intercellular collagenous tissue varies with the intensity of the scurvy. Ascorbic acid is found in measurable quantities in all tissues, notably in plasma (normal 0.8 to 1.2 mg. per cent); and white cells and platelets (25 to 38 mg. per cent). If no ascorbic acid is found in cells and platelets a dangerous deficiency of vitamin C is present, and in such a state operation is extremely dangerous

because no sutured areas will securely heal. This is particularly important in chest surgery with reference to healing of bronchial stump and gastro-esophageal anastomosis. Patients with chest complaints who come to surgery usually have low ascorbic levels even before surgery. In a series of 22 patients, the average was only 0.15 mg. per cent. The operation by itself considerably reduces the ascorbic levels still lower, according to the severity of the surgical procedure, and this level remains low according to postoperative complications and treatment. A single determination of the ascorbic acid level of plasma is not the most reliable index of the vitamin C condition of the patient because of fluctuations in the diet. A determination of the vitamin C saturation, testing plasma levels during five hours after an intravenous dose of 1 g. of ascorbic acid is better. In cases of deficiency the plasma level quickly returns to zero. When the tissue concentration is higher, the level of the plasma will fall more slowly. Except in cases of severe deficiency, as found in patients with stenosis of the esophagus, it is possible to maintain an almost normal plasma ascorbic acid level before and after operation by administration of 1,000 mg. of ascorbic acid every day (best given in divided doses). Every patient with a chronic surgical chest condition should be given high doses of ascorbic acid before and especially after important surgical procedures to ensure adequate wound healing. [An excellent bibliography is appended.]—*The Importance of Ascorbic Acid (Vitamin C) in Chest Surgery, E. de Jesus Zerbini, J. Thoracic Surg., August, 1945, 14: 309.*—(W. M. G. Jones)

**Postoperative Chest Complications.**—One hundred herniorrhaphies and one hundred meniscectomies in males of similar ages were compared. Half of each group were performed with ether anesthesia and half with gas and oxygen. There was no difference between the different anesthesia groups, but there was a greater number of chest complications in the herniorrhaphy group, irrespective of the anesthetic agent used.—*Postoperative*

*Chest Complications: Controlled Study in Hernia and Meniscectomy Operations, F. R. Gusterson, Lancet, October 6, 1945, 249: 431.—(J. Gerstein)*

**Cerebral Abscess from Chest Infections.**—The rôle of the spinal veins. It is claimed that the high incidence of cerebral abscess in chronic chest infections is due to the transportation of infected material from chest to brain by the spinal veins which are valveless, permitting blood flow in either direction. Points of value in arriving at this conclusion are that these cerebral abscesses are found predominantly in males; the disease rapidly reaches a fatal termination; it follows chronic disease of either lungs or pleurae; surgical intervention increases the danger of cerebral abscess; similar abscesses seldom are found in other parts of the body. To explain these associations it was for many years taught that cerebral abscesses were produced by septic emboli from pulmonary septic foci. However this theory does not fit all the facts. Septic emboli may lodge anywhere; they produce signs of embolism and result experimentally only in meningitis. Cerebral abscesses following empyema do not fit this theory. Other current theories are discussed. It was noted that a large number of malignant cerebral abscesses are found in carcinoma of the breast — 23 per cent as compared with 35 per cent from the bronchus. This suggested a thrombotic origin via the bronchial and intercostal veins which drain both the lung and chest wall into the azygos veins. Veins from around the spinal cord also drain into the azygos system. These veins communicate above with the venous sinuses of the skull. Injection experiments on cadavers showed that radiopaque material injected into an intercostal vessel readily entered these spinal veins. Animal experiments (in cats) were, however, not successful. It is believed that thrombi in intercostal vessels are usually carried to azygos vessels and thence to the superior vena cava and to pulmonary bed without ill effect. When, however, there is a reversed flow in the spinal

veins, then the thrombi may enter this system and be carried directly to the brain. These conditions will be present while coughing, or straining at stool, or when the patient is lying flat on his back. By this theory, all the facts of the case mentioned are explained: the exclusive involvement of the brain is easily understood; operative interference is dangerous due to the close proximity of infected tissue to an intercostal vein; in acute conditions the veins in chest wall are not involved; the greater activity of the chronically sick encourages dislodgement of thrombi; lung abscess and bronchiectasis only produce this condition when because of chronicity or surgical treatment there are adhesions and pathways to involve the intercostal system. The clinical importance of this theory is that when a rib resection is performed for surgical drainage the intercostal veins should be ligated so that there will be no chance of a process of thrombosis spreading to them.—*The Etiology of Cerebral Abscess as a Complication of Thoracic Disease, J. L. Collis, J. Thoracic Surg., December, 1944, 13: 445.—(W. M. G. Jones)*

**Wounds of Mediastinum.**—Through-and-through bullet wounds of the mediastinum are grave, but young and vigorous men often survive if they can be treated early. The treatment consists of absolute rest and heavy sedation with morphine for the first forty-eight hours. Not even the clothes are removed, but plasma or blood is given, as is intramuscular penicillin every three hours. These patients usually have a hemothorax which requires aspiration, but it is considered unwise to aspirate within the first forty-eight hours for fear of disturbing the pressure relations in the thorax and thus encourage bleeding from severed pulmonary or mediastinal vessels. Infection of the hemothorax did not occur in the 3 cases observed. One case had a hemopericardium as well. Instillation of 40,000 units of penicillin into the pleural cavity followed each aspiration of the hemothorax.—*Through-and-through Bullet Wounds of the Mediastinum, T. S. Norris,*



*Lancet*, October 13, 1945, 249: 464.—(H. Marcus)

**Duodenal Obstruction by Tuberculous Lymph Nodes.**—It is well known that varying degrees of compression of the duodenum may be caused by masses of enlarged lymph nodes as well as by lesions occurring in the head or body of the pancreas. A case is, therefore, reported in which severe constriction and partial obstruction of the duodenum were observed with relatively little widening of the duodenal curve. A twenty-three year old colored youth, previously hospitalized for right pleural effusion, was admitted to Mt. Sinai Hospital two years later, complaining of epigastric pain, vomiting and progressive weight loss. Gastro-intestinal X-ray series revealed definite gastric retention (75 per cent); constriction of pylorus, duodenal bulb, proximal portion and second portion of the duodenum. Slight widening of the duodenum was also present. Tuberculin tests were negative and sputum and gastric contents revealed acid-fast bacilli. While the findings fulfilled the criteria for diagnosis of carcinoma of the head of the pancreas, the long course and absence of jaundice tended to rule this out. Surgery, undertaken to relieve the obstruction and establish a diagnosis, confirmed the diagnosis of enlarged lymph nodes. Biopsy of one of the nodes revealed a hyperplastic tuberculosis with caseation.—*Duodenal Obstruction Due to Tuberculous Lymphadenitis*, R. H. Marshak & D. Dreiling, *Radiology*, May, 1945, 44: 495.—(G. F. Mitchell)

**Eosinophilic Infiltrations.**—It is generally conceded that eosinophilic pulmonary infiltrations, as first described by Löffler, can be caused by a variety of allergens in patients who have a tendency to react with allergic manifestations. Autopsy reports of the condition are few, but those available show that the pulmonary lesions are eosinophilic bronchopneumonias with or without bronchial involvement. Pneumococci or other microorganisms cannot be regularly demonstrated in these lesions. Recent reports also make

it likely that eosinophilic infiltrations need not be restricted to the lungs. Infiltrations in the liver have been described in one case, and another case had eosinophilic infiltrations in the epididymis. Eosinophilic infiltrations are apparently an expression of a general hypersensitive state and, because of the benign nature of the condition and the ease with which even relatively small alterations can be demonstrated in the lungs, the disease was previously thought to be restricted to the lungs. In the author's 4 cases, the pulmonary lesions were but one manifestation of a generalized disease. High blood eosinophilia was present in all 4 patients. One case showed localization in the ear with a discharge containing many eosinophiles and with central nervous system signs with demonstration of eosinophiles in the spinal fluid. This patient also had signs and symptoms of myocardial disease and joint manifestations. Two patients had a past history of typical bronchial asthma. The pulmonary lesions were usually fairly extensive and bilateral. In 2 cases pneumococci were demonstrated in the sputum repeatedly and these patients responded well to the administration of sulfathiazol. Sputum culture for pneumococci is always indicated in patients suspected of eosinophilic pulmonary infiltrations in as much as chemotherapy seems to exert a specific beneficial effect in such cases.—*Ein Beitrag zur Frage nach der Pathogenese, Ätiologie und Therapie der eosinophilen Lungeninfiltrate*, N. Alwall, *Acta med. Scandinav.*, November 3, 1945, 115: 350.—(H. Marcus)

**Transient Pulmonary Infiltration with Death.**—The condition of transient pulmonary infiltrations does not constitute a sharply defined pathological entity. Löffler distinguished between transient infiltrations of tuberculous etiology and those in tuberculin negative persons. Eosinophilia is not necessarily a predominating sign; transient infiltrations occur without eosinophilia. Conversely, an eosinophilia may exist in tuberculous infiltrations possibly on a hyperergic basis.

The allergic element has come more in the foreground and most investigators are inclined to believe that the infiltration of the lungs is due to an allergic reaction, related to asthma and urticaria, in hypersensitive persons. In an adult with an asthmatic history of one year, X-ray films revealed an infiltration of the right lung. He had an eosinophilia of 70 per cent. The patient died about five minutes after using, for the first time, a spray containing 10 per cent adrenalin. Post mortem X-ray films of the lungs showed barely perceptible remains of the infiltration, twenty days after its detection. Histological examination showed an abundant infiltration by plasma cells and lymphocytes at the involved site. At some places the lung structure was obliterated and the alveoli distended by different types of cells with conspicuous eosinophilia. There was an associated patchy hyperemia and edema. The cause of death was felt to be a rapidly arising ventricular fibrillation caused by the local effect of adrenalin on the lungs and reflex action on the heart resulting in fibrillation.—*A Case of Transient Pulmonary Infiltration with Eosinophilia, with Fatal Issue after Treatment by Adrenalin Spray for Asthma, O. J. Broch, Acta med. Scandinav., March 18, 1948, 113: 311.*—(E. R. Loftus)

**Tropical Eosinophilia.**—Fifteen cases of tropical eosinophilia are reported. The patients' main complaint was an irritating, non-productive cough; pain in the chest and dyspnea were also frequently complained of, but asthma was observed in only one patient. Twelve of the 15 patients were afebrile. Physical signs were unreliable. It appears that the duration of the disease, with exacerbations and remissions, may be as long as ten years. To the diagnosis, the presence of eosinophilia, is obviously essential. In most cases the onset of tropical eosinophilia is preceded by an infection of the respiratory tract without eosinophilia; this infection lingers on, sensitizes the patient in some way, and is eventually superseded by the varied picture of tropical eosinophilia. Exacerba-

tions are accompanied by a rise in eosinophils. X-ray films of the chest show a diffuse mottling in many cases, resembling early pneumoconiosis; unfortunately, this classical picture cannot be found in all cases. Sometimes only congestion can be seen or a pneumonic infiltration may be present; the hilar shadows are usually increased. There is no definite evidence of a relationship between tropical eosinophilia and syphilis, malaria, tuberculosis or helminthiasis. In the treatment arsenicals are commonly used, with good effect, although exacerbations lasting thirty-six to forty-eight hours are frequently observed. The lung lesions and eosinophilia apparently respond to sulapyridine, too; how either of these drugs exerts its effect is not known, but their efficacy suggests that the disease is of infectious origin. Whether or not it is a new disease entity is still a moot question.—*Tropical Eosinophilia: A Report on Fifteen Cases, H. B. Lal, Indian M. Gaz., January, 1945, 80: 80.*—(P. Lowy)

**Experimental Anaphylactic Pulmonary Lesions.**—A peculiar type of pneumonitis occurs in some cases of acute rheumatic fever. The specific nature of these lesions can be recognized only histologically. Briefly, the changes consist primarily in focal damage to the small blood vessels, particularly the alveolar capillaries, with attending capillary thrombosis, exudation and hemorrhage. In some areas coagulation and inspissation of the fluid may produce a hyaline membrane that lines the respiratory bronchiole and its alveoli. No bacteria can be demonstrated in the tissue either by culture or stain. The lesions are decidedly focal, frequently involving only a small segment of a vessel. Confluent foci, however, may result in considerable areas of involvement. It has been previously shown that focal lesions, histologically like those of rheumatic pneumonitis, occur in the lungs of non-rheumatic patients who develop anaphylactic reactions to the sulfonamides. This basic identity of the pulmonary lesions of rheumatic fever with those resulting from

anaphylactic hypersensitivity in man led to the study of the lungs of rabbits in which lesions, strikingly similar to those of rheumatic carditis, had resulted from anaphylactic "serum sickness." In the present paper the findings of that study are elaborated in an attempt to support the view that the lesions of rheumatic fever are due to hypersensitive reactions. Fifty-six rabbits were sensitized to horse serum, egg albumin or to a mixture of these. The antigen was administered intravenously. Sections of the lungs of all the rabbits were studied. Ten of the animals showed definite lesions. Three had been sensitized with serum, one with a mixture of serum and egg albumin and 6 with egg albumin alone. The number of injections varied from one to 6 over a period of from one to three months. The time between the last injection and death varied from immediate shock to ten days. The pulmonary lesions found present in these animals exhibited, in varying degrees, focal capillary damage of the type that characterizes the pneumonitis of acute rheumatic fever and of sulfonamide hypersensitivity in man. This experimental finding is offered as further support of the view that the various lesions of rheumatic fever are dependent on anaphylactic hypersensitivity. (With 11 plates).—*The Experimental Production of Anaphylactic Pulmonary Lesions with the Basic Characteristics of Rheumatic Pneumonitis*, J. E. Gregory & A. R. Rich, *Bull. Johns Hopkins Hosp.*, January, 1946, 78: 1.—(J. S. Woolley)

**Biotropic Pneumonopathy.**—The author has observed several cases where in the course of pneumonia, after the resolution of the pneumonic focus, pulmonary consolidation was present for days or weeks. This condition is called by the author "biotropic pneumopathy." It is caused either by syphilis or by tuberculosis. Five observations are described, of which 4 responded to treatment with bismuth and salvarsan. Only one had a positive Wassermann test but the successful treatment with antiluetic is proof enough of the syphilitic origin of the pneumonopathy.

One case was caused by an old tuberculosis. These pneumonopathies are really fibrous reactions of the interstitial tissue of the lung which start at the same time as the pneumonia and not as a result of it. But while the pneumonia resolves in about eight days the biotropic interstitial reaction which causes a density in the X-ray film persists. X-ray examination shows evidence of thin fibrous tracts which may produce a deviation of the trachea and a shift of the heart. The biotropic pneumonopathy should not be confused with post-pneumonic intraalveolar fibrosis which is always of very bad prognosis.—*Pneumopatia biotropica en el curso de la pneumonia*, M. Gonzalez Olacchca, *Rev. méd. peruana*, June, 1945, 18: 189.—(W. Swienty)

**Asbestosis.**—The presence of asbestos bodies in the sputum is proof of a pathological tissue reaction in the lungs. The asbestos body consists of an asbestos fiber surrounded by hemosiderin. In contrast to silicosis, asbestosis usually does not show characteristic changes on the roentgenogram. Four case histories are presented: (1) A 42 year old man, who had worked in the asbestos-industry for eighteen years, complained of productive cough and dyspnea of three years' duration. The sputum contained asbestos bodies and no tubercle bacilli. The chest roentgenogram had an appearance similar to one in silicosis. This is the only case of asbestosis without tuberculosis that the author saw. (2) A 66 year old man, who had worked in an asbestos mill for twenty-two years, complained of cough of fifteen years' duration and increasing dyspnea. The findings on X-ray examination were the same as in silicosis. The patient developed renal tuberculosis and diabetes. (3) A 67 year old man, who had worked in an asbestos mill for forty-eight years, showed asbestos bodies and tubercle bacilli in the sputum. The autopsy proved the presence of tuberculosis and asbestosis. (4) A 57 year old man, who had worked in the asbestos industry for twenty-five years, died from lung carcinoma and asbestosis, proven by autopsy. The

chest roentgenogram had shown no sign of asbestosis, nor had there been any functional pulmonary damage due to asbestosis.—*Quelques considérations sur l'amiantose*, L. Rousseau, *Laval méd.*, January, 1946, 11: 57.—(G. C. Leiner)

**Broncholithiasis.**—Broncholiths originate from calcified caseous tuberculous areas in the pulmonary parenchyma or lymph nodes, from inspissated pus of a lung abscess or an empyema, from calcified cartilages of the trachea and main bronchi. Ten cases of broncholithiasis were observed. Symptoms were cough, expectoration of calculi, substernal pain, hemoptysis, later suppuration with production of purulent fetid sputum, atelectasis. All patients were bronchoscoped. Eight patients expectorated a broncholith spontaneously; in 5 patients one or more broncholiths were removed by bronchoscope. In 6 cases the place of the erosion was identified bronchoscopically by inflammatory stenosis of the bronchus. The localization was the right middle lobe in 5 cases, the right lower lobe in 3, the left upper and the left lower lobe in one each. Follow-up bronchoscopic examination was done over an average period of twenty-five months. In no case was permanent cicatricial narrowing of the bronchus found. Residual cylindrical bronchiectasis is the most common complication.—*Broncholithiasis: Report of Ten Cases*, J. R. Fox & L. H. Clerf, *Ann. Int. Med.*, December, 1945, 23: 955.—(G. C. Leiner)

**Hodgkin's Disease and Tubercle Bacilli.**—The present study is an attempted reevaluation of the etiologic rôle of human, bovine and avian tubercle bacilli in Hodgkin's disease. Six varieties of culture media and a series of chickens, guinea pigs and rabbits were inoculated with fresh macerated lymph node and splenic tissue emulsion. Thirty lymph nodes and 3 spleens were obtained surgically from 33 patients with histologically proved Hodgkin's disease and 10 control chickens were inoculated with tissue suspensions from other diseases. Eight rabbits, 4

control and 4 experimental, were inoculated in a similar manner. A group of 20 guinea pigs was sensitized with 1 to 3 mg. of killed tubercle bacilli (dry weight) according to the method of L'Esperance eight to twelve days previous to inoculation with Hodgkin's tissue suspension. Ten additional guinea pigs received only killed tubercle bacilli and were used as controls. In no instance were tubercle bacilli found except in the case of histologically, bacteriologically and clinically proved tuberculosis.—*Studies in Hodgkin's Syndrome: III. The Relationship of Tubercle Bacilli to Hodgkin's Syndrome*, H. A. Hoster, C. A. Doan & M. Schumacher, *J. Lab. & Clin. Med.*, August, 1945, 30: 675.—(F. G. Petrik)

**Intrathoracic Malformations.**—In recent years an increasing number of congenital cystic lung changes have been described. Their importance has been somewhat altered from the earlier pathological anatomical interest to increased diagnostic interest and in many cases to therapeutic interest. The cause of the condition is probably not a question of a genetic unit; however, the prevalent explanations on the basis of fetal bronchiectasis, congenital lymphangiectasis, lung or bronchial adenoma are inadequate. It seems that the more neutral term of congenital cystic lung on a malformation basis is more applicable. The variation in the number and size of the cystic elements is dependent upon the stage of fetal development when the disturbance in development and the degenerative process occur. There may be an association with malformations in other organs such as the kidneys. Other authors have reported interesting cases in which diffuse cystic lung changes appeared simultaneously with a tuberous cerebral sclerosis. A case of bilateral disease is described in which the symptoms did not make their appearance until 14 months of age. The diagnosis was made by roentgenography disclosing a marked bullous emphysema. The condition was incompatible with life. A second case is reported in which the diagnosis of pleural

effusion was made in a one and one-half year old boy. The physical findings on admission indicated a massive pleural effusion, substantiated by X-ray findings. Thoracentesis revealed thick greyish, sterile fluid which promptly reformed. A thoracoscopy revealed a large irregular tumor which was tentatively diagnosed as teratoma. A thoracotomy revealed a large cystic tumor which filled the left thoracic cage and caused deviation of lung and mediastinum to the opposite side. The report by the pathologist indicated that the tumor contained fat globules and mucus-secreting glands. The overall picture resembled that of fibroadenoma of the breast. The consensus was that this tumor was probably a matter of a simpler local malformation, though the possibility of a dermoid tumor could not be excluded.—*Intrathoracic Malformations in Young Children*, B. Soderling & R. Thune, *Acta med. Scandinav.*, February 12, 1943, 113: 239.—(E. R. Loftus)

**Diaphragmatic Malformation.**—A four week old boy died in marked dehydration after continuous vomiting from birth. At autopsy there were found a stenosis of the cardia of the stomach and bronchopneumonia, which were responsible for death, and an unrelated anomaly of the diaphragm. The right pleural cavity was divided by a membrane extending from the base of the sixth rib forward, in arch like form, to the angle of the inferior vena cava and pericardium, where it joined with the diaphragm. The base was transparent, but the free margin contained striated muscle and a small nerve and blood vessels. It is this which makes the author feel that the anomaly is one of the diaphragm and not of the pleura. The cause is unexplained.—*Eine seltene Zwerchfellmissbildung (partielle einseitige Doppelbildung)*, P. Haeblerlin, *Schweiz. med. Wchnschr.*, June 9, 1945, 75: 510.—(J. Gerstein)

**Diaphragmatic Hernia.**—A diaphragmatic hernia is a prolapse of part or all of the stomach, with or without the end of the

esophagus, through a gap in the diaphragm. This gap is usually the esophageal hiatus. The hernial sac is usually covered with peritoneum, in which case it lies behind the heart. There are two types, the incomplete para-esophageal hiatus hernia and the complete hiatus hernia. The former contains only a small part of the stomach and none of the esophagus. The latter contains all of the stomach or a large section thereof, and the terminal end of the esophagus. Important in the formation of such hernia are increases in abdominal pressure, as in meteorism, congenital or acquired factors increasing the size of the diaphragmatic gap, traction by the longitudinal muscle of the esophagus on the cardiac end of the stomach, especially in prolonged vomiting, and interference in the growth of the esophagus. When the esophageal hiatus is weakened the difference in abdominal and thoracic pressures occurring with respiration becomes important. There are often no symptoms, with discovery coming at autopsy. The most common ones are pyrosis, retrosternal pain and a feeling of oppression. These occur most often at night or in early morning, are aggravated on lying down and are improved by standing up or moving around. Less frequent are symptoms of cardiac disease, anemia, ulcer in the herniated segment and strangulation.—*Zur Anatomie, Pathogenese und Klinik der Zwerchfellbrüche des Magens und des Oesophagus*, H. Weber, *Schweiz. med. Wchnschr.*, February 10, 1945, 75: 117.—(J. Gerstein)

**Diaphragmatic Hernia.**—Diaphragmatic hernia and eventration are easily confounded clinically as well as roentgenologically. Sometimes, it is impossible to make a correct diagnosis. The hernia always occurs through a normal or pathological opening of the diaphragm through which contents of the abdomen escape into the thoracic cavity. Eventration is due to relaxation of the muscle which causes a high elevation of a portion of the diaphragm, the abdominal viscera being within the abdominal cavity. The authors

have operated on 5 cases of nontraumatic hernia and have observed 3 more cases. Only in one case was a clinical diagnosis made, in all others it was made by X-ray. A very rare location of the diaphragmatic hernia is the subcostosternal space limited by the sternum and the costal and sternal fibers of the diaphragm (foramen of Morgagni) and by the muscle bundles inserted in the posterior portion of the base of the xyphoid process (foramen of Larrey). These are generally congenital hernias and sometimes are combined with a hernia of the esophageal hiatus. Often there is absence of the left crus of the diaphragm which may account for a communication with the aortic hiatus. The varieties of the most frequent type, the esophageal hiatus hernia, are: (1) a short esophagus with cardia and fundus of the stomach in the thorax; (2) the cardia in normal position but the fundus in the hernia; (3) a long esophagus with cardia and fundus in the hernia. The differential diagnosis has to exclude traumatic hernia and eventration. In the latter case the leaf of the diaphragm is seen in the X-ray film above the abdominal viscera and the stomach is generally U-formed, whereas in a true hernia it has hour-glass appearance. Paralysis of the phrenic nerve causes a descent of the diaphragm in eventration, whereas in the true hernia there is no change. Pneumothorax and pneumoperitoneum may be of importance for the differential diagnosis. The authors did not use phrenicectomy for diagnostic purposes as they believe that the innervation of the diaphragm is of utmost importance to prevent recidivation of the hernia. An upper left paramedian laparotomy was done as it was felt that the abdominal approach presents a smaller risk than the thoracic. The hernia sac was not resected and the immediate and late results were satisfactory.—*Hernia diafragmatica*, R. Vargas M. & A. Larach N., *Rev. méd. de Chile*, August, 1945, 73: 687.—(W. Swicnty)

**Embolectomy in Pulmonary Embolism.**—The operation described by Trendelenburg

for embolectomy of the pulmonary artery or its main branches was used in a case of massive pulmonary embolism. A 43 year old woman had a long abdominal operation for carcinoma of the colon. She apparently made a good recovery, but two weeks following the operation she suddenly developed all the signs of pulmonary embolism and was moribund within twenty minutes from the onset of clinical symptoms. The operation described by Trendelenburg was employed, and many large clots were removed from the main and from the right and left pulmonary arteries. The patient made a good recovery in spite of the fact that respiration had been absent preoperatively for fifteen minutes, and cardiac action had stopped for sixty seconds. Twenty-one days later, when the patient had completely recovered, another embolization occurred. A second Trendelenburg operation was performed and this was initially successful. However, the patient died seventeen hours postoperatively due to aspiration pneumonia. Apparently the brain had been damaged irreparably by the temporary anoxia, and the patient never recovered from coma. At autopsy large fresh thrombi were found in both femoral arteries. The operative site, in the pulmonary artery was free from clot, and only small emboli were found in branches of the pulmonary artery. The brain showed microscopic areas of degeneration of ganglion cells.—*Erfolgreiche Trendelenburg'sche Operation einer fulminanten Lungenembolie*, R. Nicole, *Schweiz. med. Wchnschr.*, December 8, 1945, 75: 1080.—(H. Marcus)

**Pulmonary Embolism.**—A total of 162 episodes of pulmonary embolism in 108 patients is analyzed. Pleuritic pain occurred sixty-six times in 54 patients; pulmonary consolidation, sixty-seven times in 59 patients; episodes of dyspnea, fifty times in 43 patients; anginal pain, thirty-seven times in 26 patients; shock, forty-two times; sudden loss of consciousness, eleven times; tachycardia, sixty-two times in 53 patients; fever as sole manifestation, three times; sudden death, in 3 patients; unsuspected pulmonary

embolism was found at autopsy in 3 patients who had died of other causes. The source of the embolism in 90 cases was the veins of the legs (only 60 of these had definite evidence of thrombophlebitis); in 2, the arm veins; in 7, pelvic veins; in 9, mural cardiac thrombi. Predisposing factors were operations in 64 cases; nonsurgical disease in 14 cases; trauma to an extremity in 6 cases; peripheral vascular disease with thrombophlebitis in 24 cases. In 50 per cent in which electrocardiograms were taken the pattern of acute cor pulmonale was found. Leucocytosis and slight increase of the icterus index were frequent.—*Clinical Syndrome in Patients with Pulmonary Embolism*, E. L. Sagall, J. Bornstein & L. Wolff, *Arch. Int. Med.*, October, 1945, 76: 234.—(G. C. Leiner)

**Infarct Cavity.**—A patient with mitral stenosis and insufficiency was admitted to the

hospital in heart failure. Fluoroscopic examination of the chest showed a dense infiltration in the right middle lobe, in addition to the characteristic cardiac configuration. The infiltration was at first thought to be a primary or secondary tumor, but later on breakdown and cavity formation was observed in that region. The cavity healed without leaving a trace. Although there was no history of the typical symptom complex of pulmonary infarction, the absence of pathogenic microorganisms in the sputum, including the absence of acid-fast bacilli, and the quick disappearance of the cavity in a known case of mitral stenosis in heart failure, make the diagnosis of infarct cavity extremely likely.—*Infarktkaverne der Lunge mit Ausgang in Heilung*, A. Urech, *Schweiz. med. Wchnsehr.*, November 17, 1945, 75: 1004.—(H. Marcus)

## HEART DISEASE IN THE CASE-FINDING PROGRAM<sup>1</sup>

HOWARD F. WEST<sup>2</sup>

Hundreds of X-ray films of the chest are being recorded daily throughout the nation and are accepted as the most accurate and rapid procedure for detecting early tuberculosis. Of necessity an image of the whole chest is recorded, its bony structure and its contents. The central figure on the film, the portion that first catches the eye, is the silhouette of the heart and great blood vessels. In studying the lung fields the eye of the interpreter must of necessity traverse the areas on either side of this central shadow. How indifferent should he be to this very obvious portion of the film?

One of the important tools of the cardiologist is the X-ray. By means of this medium he gains important information as to the size, shape, position and general contour of both the heart and the great blood vessels leading to and from it. He may also obtain evidence of pulmonary disease resulting from impaired heart function which of itself may materially handicap circulatory efficiency. Structural abnormalities of the chest may be demonstrated which by displacement or distortion of the heart or the great vessels add to its functional load.

It is true that since the heart is a globular organ consisting of four chambers, a complete X-ray examination should also include fluoroscopy and oblique views. The flat films alone, however, showing a composite silhouette of the heart as a whole as well as parts of the aorta, the pulmonary artery and larger veins yields information of very considerable worth.

Disease of the heart is shown on these films whenever the damaging process has produced an enlargement of any or several of its chambers or of the great vessels, thus changing the shape of the composite shadow or has increased the over-all size by hypertrophy or dilatation or by combinations of these factors.

Congenital anomalies may alter the configuration of the heart shadow because of structural variation, or the mechanical defects may cause partial or total enlargement because of continued interference with normal blood flow.

Chronic valvular disease, whether as the result of syphilis or rheumatic fever, is a very important cause of changes in the contour and size. Continued interference with the normal progression of the blood stream leads to dilation of the chambers involved and to thickening or hypertrophy of the chamber wall. Many of these lesions produce rather characteristic variations from the normal X-ray appearance.

Continued overwork, in the absence of congenital or valvular defects, will produce an increase in heart size and modify its shape. The most common cause of such strain is chronic arterial hypertension. The greater part of the increased load is borne by the left ventricle, the walls of which thicken and eventually dilate to varying degree.

<sup>1</sup> Presented before the Medical Section at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 12, 1946.

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Arteriosclerosis, hypertension and syphilis each tend to produce changes in the aorta, dilation, elongation or aneurysm, which may be noted on the film.

In the arteriosclerotic group calcification of the aorta may be seen and, less commonly as the result of chronic disease, one may note calcification of the valves or of the pericardium.

Thickening of the pericardium as the result of chronic pericarditis, at times due to tuberculosis, will enlarge the heart shadow as will acute pericarditis with effusion or purulent exudate. The latter group of patients will in all probability be too ill to be included in routine surveys.

An acute observer, alert to the X-ray manifestation of heart disease, will note at least the more obvious indications of cardio-vascular abnormalities as rapidly as he can detect evidence of minimal tuberculosis.

It is generally accepted that an enlarged heart is an abnormal heart, though the converse is not necessarily true. A person may have very serious arteriosclerosis of his coronary arteries, for instance, without an increase in heart size or other distortion of the cardiac outline unless this difficulty is accompanied by hypertension or, more rarely, other disease processes. This condition, coronary artery disease, unfortunately, is a common cause of disability and death.

It is with the interpretation of border-line enlargement that the roentgenologist has the greatest difficulty. The size of the normal heart varies with such factors as body size, age and sex. Numerous attempts have been made to establish exact measurements by which departures from the normal in size may be detected. Unfortunately, because of the normal variations, the error in even the best system of measurement can hardly be less than 10 per cent.

The standard procedure of cardiologists for the estimation of heart size is to employ a 14 x 17" film at 6 feet or 2 meters distance from the target in order to avoid as much as possible the magnification of the heart image caused by divergence of the X-ray beam (1).

Modern mass surveys, however, employ small films photographing the fluoroscopic image and thus record the distortion inherent in the short target-screen distance. Gross abnormalities of the heart image are as easily detectable on these films, however, as they are on the standard 14 x 17". The interpretation of less than gross increase in heart size, however, has introduced a serious problem, especially since no standard measurements have as yet been adopted generally for use with small films, and also because there is doubt in the minds of many roentgenologists as to the wisdom of attempting to apply exact measurements for the detection of minor degrees of pathological enlargement. This doubt is due to the considerable variation in normal heart size mentioned above.

In a carefully conducted study by Drs. William Paul Thompson and Joseph Jellen of the Los Angeles Heart Association, soon to be published, criteria for the measurement of heart size on the 4 x 5" film have been established. These measurements reveal a remarkably close agreement with the Ungerleider tables, and moreover demonstrate that the frequently used cardio-thoracic ratio is almost as valid on the 4 x 5" film as with the standard method. Gubner and Ungerleider (2) have also reported an ingenious and simple device for determin-

ing heart size measurements on miniature films of any size. There are certain technical difficulties with this latter method, however, that might well impede its usefulness in rapid surveys with miniature films.

It is not proposed that all films should be measured. Measurements need be used, if deemed practical, only with those films concerning which the reader is doubtful about the presence of pathological heart enlargement.

For the past three years the Heart Division of the Los Angeles Tuberculosis and Health Association has participated in the case-finding project of the Industrial Health Program. From May, 1943 through February, 1946, a total of 63,398 persons have been X-rayed. In this series the interpretation of suspected tuberculosis was 2.7 per cent and of suspicious heart abnormalities, 2.0 per cent. A follow-up with complete clinical examination would be necessary to determine the accuracy of the survey interpretations. This has not been possible for the entire series. However, an analysis by the Los Angeles Association of a smaller series has been made recently. The 4 x 5" films taken of 8,933 industrial workers during a five-month period showed 414 total suspicious films. Of these 151 were suspicious of cardiac abnormality. At the time of the analysis, 116 persons, 77 per cent, had been reexamined and a final diagnosis obtained. Of these diagnoses, made by private physicians and clinics, 87 were positive and 29 were negative for cardiac disease. That is, there was approximately 75 per cent clinical confirmation of the cardiac interpretations made by the film readers (radiologists and chest specialists). This degree of accuracy may be compared with the results of Edwards (4), who reported a confirmation of 80.8 per cent of suspicious X-ray findings in a larger series in the Harlem survey.

It is to be remembered, however, that in each of these surveys no consistent attempts at actual measurements of heart size were made. The variation in the judgment of the film readers are naturally reflected in the final confirmatory examinations. The more conservative the film interpretation the fewer mistakes will be made, but a variable number of persons having heart disease but revealing less than gross enlargement will be overlooked. The Thompson and Jellen studies were under way while the Los Angeles survey was being made and analyzed.

Other reported surveys by group X-ray methods have indicated the finding of suspected heart disease among different segments of the population, varying from less than 1.0 to over 7.5 per cent (5). It has been estimated that at least 50 per cent of those with proved circulatory disease have been unaware of their difficulty prior to the survey studies.

Since a considerable portion of unsuspected heart disease can be recognized by essentially the same technique used in finding early tuberculosis, it is important to decide quickly what use can and should be made of this information. The person with unrecognized tuberculosis endangers his fellow man, while the one with heart disease seldom does, yet the latter group of diseases causes many more deaths, much more disability, and the social and economic problems involving the community as a whole are tremendous. In reporting the results of X-ray examinations shall we be content with "no X-ray evidence of tuberculosis"

leaving a considerable number of those surveyed unaware of suspected heart disease? That, obviously, is hardly fair. On the other hand, if we do report our suspicion of heart disease, we must be prepared to do something about it and that promptly. We must see to it that a complete clinical follow-up is available to confirm or rule out the suspicion gained by this single bit of information which cannot be considered any more final than the X-ray suspicion of tuberculosis. We must see to it that sound medical advice is available so that those with positive diagnosis will know how to conduct their lives so as to avoid suffering and disability to the greatest possible extent. At the same time we must be exceedingly careful not to frighten too many people with reports of suspected heart disease, based upon inept or too enthusiastic reading of the films.

For accuracy in film interpretation the subject must be accurately centered and the exposure made at mid-inspiration for, as the diaphragm rises and falls, the position of the heart changes and an erroneous impression of its size may be obtained. The reader of the film must of necessity be as familiar with evidence of heart abnormality as with indications of pulmonary disease.

Since X-ray surveys are proceeding with considerable speed throughout the country, it is suggested that the National Tuberculosis Association and the American Heart Association establish a joint committee at the earliest possible time to consider the problem of joint case-finding in its entirety. First of all this committee should agree upon a fundamental philosophy. If it is decided that the method is of practical value then it should adopt adequate standards of procedure, technical, clinical and social, for the guidance of local groups in the field. Much material, including previously established criteria for use with standard X-ray methods, is available for consideration. In addition to those surveys in which abnormal cardiac images have been recorded, the military services have made hundreds of thousands of chest roentgenograms, including miniature films, and all suspicious findings, including the heart, have been given full clinical evaluation. Much of this information should be available for further study and guidance. The United States Public Health Service should also be prepared to furnish valuable experience and advice.

Local groups and health departments are attempting to develop facilities for the interpretations of heart disease, as well as tuberculosis by means of survey chest films. If there is practical and useful merit in the procedure, standards should be set up on a national level for the guidance of all.

#### SUMMARY

An X-ray film of the chest may reveal evidence of tuberculosis or evidence of heart disease. Heart disease is suggested by increase in heart size or by abnormal shape or contour of either the heart or of the great blood vessels. Roentgenograms obtained in mass surveys are being studied by various groups in order to determine their value in heart disease case-finding. It is proposed that a joint committee, composed of members of the National Tuberculosis Association and the American Heart Association, be created to consider the value of this procedure and, if approved, to establish minimal standards or criteria for such surveys.

## SUMARIO

Una radiografía torácica puede revelar signos de tuberculosis o de cardiopatía. Indican la última un aumento del tamaño del corazón o forma o contorno anómalos bien del corazón o de los grandes vasos sanguíneos. Las radiografías obtenidas en las escuelas colectivas están siendo estudiadas por varios grupos a fin de determinar su valor para el descubrimiento de casos de cardiopatía. Propónese aquí la creación de un comité conjunto, compuesto de miembros de la Asociación Nacional contra la Tuberculosis y la Asociación Americana del Corazón para considerar el valor de este procedimiento, y si se aprueba, para establecer pautas o patrones mínimos para dichas encuestas.

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## CANCER AND PULMONARY TUBERCULOSIS

### Diagnostic Problems in Patients with Cancer of the Lung in the Presence of Pulmonary Tuberculosis

BRUNO GERSTL,<sup>1</sup> FREDERICK C. WARRING, JR.,<sup>2</sup> AND KIRBY S. HOWLETT, JR.<sup>2</sup>

Coexisting cancer and tuberculosis of the lung has long been a topic of interest to both clinician and pathologist. The historical aspects of the subject are already well covered in numerous articles, several of which contain extensive bibliographical references (1, 2, 3).

In discussing the relationship between pulmonary cancer and tuberculosis, most writers (2, 3, 4, 5, 6, 7) have expressed the opinion that they are very rarely found together in one individual. Others (6, 8) believe, however, that their association is no more rare than that of other unrelated diseases, and some authors (9, 10) have suggested the theoretical possibility that one may actually predispose to the other.

Whatever one's conclusions regarding these ideas, the increasing number of reported cases with both tuberculosis and cancer indicates clearly that the clinical problem is not negligible. Yet in most of the reported cases cancer was found only at autopsy. Even if the association is purely fortuitous, there are good reasons for believing that we may well expect to see the coexistence of the two diseases in the same patient with increasing frequency. The present trend for the peak of tuberculosis morbidity and mortality, especially among men, to move into the older age groups is well known. The steadily increasing number of older men with active tuberculosis admitted to Laurel Heights in recent years has strikingly reflected this trend. This is the very group in which bronchogenic cancer is most likely to be found.

Since July, 1940, 7 cases of coexisting bronchogenic carcinoma and active pulmonary tuberculosis have been recognized at Laurel Heights among approximately 1,600 patients of both sexes and of all ages sent in with a diagnosis of pulmonary tuberculosis only. In all 7 cases either a definite or presumptive diagnosis of associated cancer was made before death. Cases diagnosed as having cancer only, and in whom the preadmission diagnosis of tuberculosis was simply regarded as erroneous, are not included.

The serious obstacles to the diagnosis of bronchogenic cancer in the presence of known active pulmonary tuberculosis are pointed out by several authors (5, 11) and are clearly apparent in our cases. These cases, together with an additional one from the Undercliff Sanatorium and another from the Cedarcrest Sanatorium are being reported not merely to add 9 cases to the cumulative list, but also to allow an analysis of factors which led to the diagnosis.

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<sup>2</sup> Laurel Heights State Tuberculosis Sanatorium, Shelton, Connecticut.

## CASE REPORTS

*A.M.:* A white male, age 64, a mine worker whose family history was negative for tuberculosis and cancer. The patient had worked in and around mines as a miner and as a laborer. About ten years of this time had been spent in anthracite mines and the remainder of the time divided among asbestos, bituminous coal and various metal mines. Approximately eight years before admission he had a small hemoptysis and was a patient for one week at a local hospital where an X-ray diagnosis of silicosis was made. After this he returned to work. Four and a half years before admission he went to the dispensary of a medical centre for a check-up. Productive cough had been present for many years. There, a roentgenogram of the chest showed bilateral, interstitial pulmonary fibrosis, bilateral fibrotic and calcific apical tuberculosis and pulmonary emphysema. The patient felt reasonably well until seven months before admission when he began to notice weakness and diurnal swelling of the ankles. He had lost 40 pounds in weight during the preceding year. Because of these symptoms he stopped work the following month.

After seeing several physicians he was admitted to the Medical Centre. Sputum was found to contain tubercle bacilli. He had pain and tenderness over the anterior aspect of the proximal third of the right radius. An X-ray film of the radius (figure 1) showed periosteal new bone formation which was interpreted as pulmonary osteoarthropathy. X-ray examination of the chest (figure 2) showed atelectasis and infiltration on the right to the third rib, with slight herniation of the upper portion of the left lung into the right hemithorax. The right middle and lower lobes were involved by a dense, homogeneous consolidation. Diffuse fibrosis with emphysema was present throughout the left lung, while at the left apex there were several small calcific densities. Laminagraphic studies demonstrated, in addition to right lower lobe consolidation, complete obstruction of the right intermediate bronchus, presumably by a solid mass. After one month the patient was transferred to Laurel Heights with a diagnosis of pulmonary tuberculosis of both upper lobes and carcinoma of the right lower lobe.

On admission to the Sanatorium the patient was emaciated and in poor condition. His temperature ranged to 100°F. There was clubbing of the fingers and slight cyanosis of the nail-beds. Small lymph nodes were palpable in both supraclavicular fossae. The heart and mediastinum were retracted to the right. A hard mass, the size of a walnut, was attached to the anterior surface of the upper third of the right radius.

A roentgenogram of the chest revealed that the infiltration and atelectasis of the right upper lobe had increased during the preceding month.

Sputum contained tubercle bacilli on two direct smears. Hemoglobin was 12.5 g. (81 per cent). Red blood cells were 4.46 millions. White blood cells numbered 24,400, with 81 per cent polymorphonuclear cells.

The admission diagnosis was bilateral silico-tuberculosis and tumor of the right lung with metastasis to the right radius. A biopsy from the lesion of the right radius revealed adenocarcinoma. His course was progressively and rapidly downhill, with expectoration of blood-streaked sputum and increasing dyspnea. He died of respiratory failure eight weeks after admission. An autopsy was performed. The patient was never bronchoscope, since his condition was obviously terminal from the time he was first seen.

*Autopsy:* The right pleural space was obliterated by firm, fibrous adhesions. Several intercommunicating, irregularly shaped cavities occupied large areas in the right upper lobe and also the lateral segment of the middle lobe. They were lined by gray, ragged, friable tissue. Numerous strands of fibrous connective tissue were seen in the remaining parenchyma. The bronchi leading to these upper and middle lobe cavities were patent. The proximal part of the right lower lobe bronchus was occluded by a polyp-like tumor.



FIG. 1. (Upper left) Case A.M. X-ray film of right radius, February 12, 1945.  
 FIG. 2 (Upper right) Case A.M. Chest X-ray film, January 16, 1945  
 FIG. 3. (Centre left) Case J.M. Chest X-ray film, October 16, 1944  
 FIG. 4. (Centre right) Case J.M. Chest X-ray film, October 2, 1945  
 FIG. 5. (Bottom) Case R.P. Chest X-ray film, December 29, 1942

A large tumor in the anterior segment of the right lower lobe had a 6 cm. central cavity, filled with necrotic tumor masses. The remaining parenchyma of this lobe showed many brownish yellow, consolidated lobules. The tumor had extended upward into the hilar nodes and radiated from there into the middle lobe.

Microscopically the tumor was an adenocarcinoma. The walls of the right upper and middle lobe cavities were composed of tuberculous granulation tissue.

In the left lung a group of proliferative tubercles were found in the apical segment. Two small, oval shaped lesions in the subapical segment of the upper lobe and in the apex of the lower lobe were composed of tuberculous granulation tissue, together with groups of tumor cells.

*J.M.*: A 51 year old molder. The patient's wife had died of pulmonary tuberculosis twenty-three years previously. There was no family history of cancer. For eighteen years the patient had worked as an iron molder and was exposed to sand dust during this period. Three months before admission the patient noticed fatigue, cough and expectoration, anorexia, pain in the right chest and hoarseness. Sputum was examined by his family physician and was found to contain tubercle bacilli. Six weeks before admission an X-ray film showed pulmonary disease and sanatorium care was advised.

On admission the patient was still fairly well nourished, although he had lost 16 pounds. Temperature was normal. A roentgenogram of the chest (figure 3) showed mottled and stringy densities in a somewhat shrunken right upper lobe. This lobe contained a 4 cm. cavity and was demarcated by a prominent interlobar fissure. There was minimal, nodular infiltration in the left apex.

Repeated smears of the sputum were positive for tubercle bacilli. Hemoglobin was 14.5 g. (94 per cent). Red blood cells were 4.21 millions. White blood cells numbered 10,400, with 71 per cent polymorphonuclear cells.

Admission diagnosis was moderately advanced pulmonary tuberculosis, involving the right upper and the left upper lobes. On bed-rest the patient showed some clinical improvement, in that he gained 20 pounds. However, at the end of the first year of residence, X-ray films (figure 4) showed increased density in the right upper lobe with upward retraction of the interlobar fissure. A cavity could no longer be seen. Pain in the right chest persisted. Whereas the sputum had been positive for tubercle bacilli during the first eleven months of residence, after that time it was negative on concentration. Because the sputum was frequently blood-streaked and occasionally "meaty" in appearance, a cell-block of sputum was made and this revealed tumor cells. Planigrams demonstrated enlarged right hilar and mediastinal lymph nodes.

At bronchoscopy, roughening of the right intermediate bronchus was found and a biopsy from this area showed oat-cell carcinoma.

The case was considered inoperable. The patient is alive and showing no unfavorable clinical change fourteen months after admission.

*R.P.*: A 63 year old Austro-Hungarian paint salesman, whose family history was negative for cancer and tuberculosis. For one year before admission the patient had had slight cough and expectoration and occasionally blood-streaked sputum. Four months before admission his cough increased and he "felt under par." His family physician had his sputum examined, but no tubercle bacilli were found. Two months before admission he had symptoms of a chest cold, with pleuritic pain on the left side and fever to 102°F. X-ray films taken by an outside physician at that time showed disease in the right lung and sputum now contained tubercle bacilli. The patient's weight had dropped from 165 to



135 pounds four months previously but had risen to 154 by the time of admission. Other symptoms at that time were cough and expectoration, streaked sputum and weakness. The trachea was found deviated to the right. There was no adenopathy.

A roentgenogram of the chest (figure 5) showed segmental atelectasis of the right upper lobe, with scattered mottling to the fourth rib. The upper mediastinum was slightly retracted to the right. On the left there was an isolated nodule at the level of the fourth rib.

Sputum, which was consistently positive for acid-fast bacilli on concentration, produced generalized tuberculosis in guinea pigs. Hemoglobin was 12 g. (78 per cent). Red blood cells were 3.78 million. White blood cells numbered 7,800, with 63 per cent polymorphonuclear cells.

Because of the positive sputum and the apical position of the disease, an admission diagnosis of moderately advanced pulmonary tuberculosis was made. On bed-rest his temperature, which had been around 100° F. daily, declined to around 99.4° F. His cough and expectoration at first decreased, although the sputum continued to be positive for tubercle bacilli. He regained another 5 pounds. In spite of this slight clinical improvement a new X-ray film after two months showed extension of atelectasis to involve the entire right upper lobe.

A bronchoscopic examination revealed bulging of the lateral tracheal wall from the right, as if from external pressure. The opening of the right upper lobe bronchus was found to be reduced to a mere slit through which bright red blood was oozing. No biopsy was taken since the mucous membrane was intact. Tumor was considered to be a diagnostic possibility but exploration of the chest was decided against because of the extent of the lesion.

According to serial films the atelectatic right upper lobe appeared more and more dense. Bronchoscopy was repeated in the ninth month of residence and a biopsy was taken from granulation tissue, which by now was present at the opening of the right upper lobe bronchus. Examination of this tissue revealed epidermoid carcinoma. Following this bronchoscopy the temperature ranged to 101° F.; he had pronounced wheezing, increased cough and expectoration and heavily streaked sputum. Two weeks before death the patient suddenly stopped wheezing and became cyanotic and markedly dyspneic. An X-ray film showed complete atelectasis of the entire right lung. Course was then rapidly downhill with weakness, dyspnea, cyanosis and irregular pulse. Death occurred eleven months after admission. Permission for autopsy was refused. The final diagnosis was: bronchial epidermoid carcinoma and pulmonary tuberculosis.

*H.D.:* A white male, age 55, a core maker with a family history negative for tuberculosis and cancer. The patient had worked as a core maker for forty-one years. Over this period of time he had been exposed to much sand dust. He had had a rectal abscess incised fourteen years before admission with healing in two weeks. Twelve years before admission he had had "pneumonia," for which he was hospitalized for eleven days. No X-ray films were taken during this illness and he does not know which lung was involved. He believes that he had a dry pleurisy on the left side at that time. Since then he had had a chronic cough, but felt well otherwise. Five months before admission the patient became conscious of fatigue, pain in the lower chest on both sides and anorexia. During the previous year he had lost 35 pounds. He stopped work seven weeks before admission because he was experiencing chills and blood-streaked sputum. Six weeks before admission he was admitted to a local hospital. There an X-ray film of the chest showed disease in the right upper lobe. Sputum was negative for tubercle bacilli.

First admission: Patient was undernourished and chronically ill. There was no adenopathy. A chest roentgenogram showed infiltration and shrinkage of the right upper lobe, with retraction of the trachea and upper mediastinum to the right. The left lung was clear.

Sputum was negative for tubercle bacilli on smear and concentration. Hemoglobin was 13.0 g. (84 per cent). Red blood cells were 3.98 millions. White blood cells numbered 11,800, with 57 per cent polymorphonuclear cells.

On bed-rest the patient was afebrile. He left against advice on the eleventh day of residence before he could be adequately studied. Diagnosis on discharge was: undiagnosed—pulmonary tuberculosis or carcinoma of the lung.

The patient rested in bed at home and his symptoms continued.

Second admission (seventeen days later): General condition was essentially the same except that he was weaker. Slight clubbing of the fingers and toes was noted.

Again the sputum was negative for tubercle bacilli, this time by concentration, culture and guinea pig inoculation. He was raising 25 to 30 cc. of muco-purulent sputum daily.

X-ray examination revealed no change in the degree of infiltration and atelectasis, but now a 4 cm. cavity could be seen in the right upper lobe (figure 6).

Bronchoscopy revealed bulging of the right lateral and anterior walls of the lower trachea—as if from external pressure. The carina was fixed, appeared thickened and transmitted the cardiac impulse. Openings of all major bronchi were seen and nowhere was there any ulceration, granulation or interruption in the continuity of the mucous membrane. No biopsy was taken, but the bronchoscopist felt that the fixation of the carina and the inward bulging of the lower trachea indicated tumor.

The patient was afebrile on bed-rest. He was discharged to his home after six weeks with the diagnoses: moderately advanced pulmonary tuberculosis, right upper lobe, inactive; secondary bronchiectasis.

Although he did not feel well he returned to work. A check-up film, five months after his second discharge, showed a small new density in the third interspace on the left. The lesion in the right lung was unchanged. Sputum was negative for tubercle bacilli. He was next seen ten days before his final admission, when he complained of anorexia, further weight loss, repeatedly bloody sputum and dyspnea even at rest. A new film revealed further shrinkage and infiltration of the right upper lobe with involvement of the middle lobe and a new cavity containing a fluid level adjacent to the hilum. Also at the right hilum was a large, dense, rounded mass surrounding and markedly constricting the right main bronchus. There was, in addition, further increase in the size of the small infiltration in the left upper lobe. A presumptive diagnosis of bronchogenic carcinoma was made.

Final admission (ten months after second discharge). The roentgenogram showed that the infiltration on the right had progressed in ten days to involve the lower lobe (Figure 7).

Hemoglobin had fallen to 11.5 g. (75 per cent). Red blood cells had declined to 3.45 millions. The white blood cells had risen to 15,700, with 72 per cent polymorphonuclear cells. One concentrated specimen of sputum was negative for tubercle bacilli. Sputum sediment was inoculated into 2 guinea pigs, one of which died from generalized tuberculosis.

Laminagrams demonstrated dense consolidation and atelectasis of the right upper and middle lobes, with the right main bronchus markedly constricted by surrounding tumor mass (figure 8). Cavitation was apparent in the lower portion of the upper lobe.

The patient ran frequent spikes of fever to 101–102°F. Dyspnea was troublesome. There was recurrent, transient edema of the arms, ankles and about the eyes. Fatal hemoptysis occurred six weeks after admission. An autopsy was performed.

*Autopsy:* The right side of the face and the right arm were edematous. The upper part



FIG. 6. (Upper left) Case H.D. Chest X-ray film, December 28, 1943.

FIG. 7. (Upper right) Case H.D. Chest X-ray film, December 6, 1944.

FIG. 8. (Centre) Case H.D. Laminagram, December 22, 1944.

FIG. 9. (Lower left) Case S.B. Chest X-ray film, April 17, 1949.

FIG. 10. (Lower right) Case S.B. Chest X-ray film, September 23, 1949.

of the right pleural space and the interlobar fissures were obliterated by firm, fibrous adhesions. Three hundred cc. of yellow, cloudy fluid were present in the lower space. On sectioning, the right upper lobe was small and contracted. Several small cavities, surrounded by necrotic parenchyma, were seen in the apex. Strands of fibrous tissue partly replaced the parenchyma. An oval shaped cavity, containing a blood clot, occupied the subapical, pectoral segment and extended into the upper portion of the middle lobe. Its wall was formed by soft, somewhat smooth tissue. A small bronchus communicated with this cavity. The lower lobe showed several large areas of necrotizing pneumonia. A few small, caseous tubercles were present in the base of the right lower lobe.

The right main bronchus was largely occluded by gray, firm tumor masses. Tumor also infiltrated two hilar lymph nodes and, extending from their upper poles, penetrated the carina and trachea. Further extension of the tumor involved the upper pericardium and the anterior mediastinum, compressing the superior vena cava and the innominate vein. This was an epidermoid carcinoma. In the left lung a group of small, proliferative tubercles was found in the lateral segment of the lower lobe.

*S.B.:* A 57 year old Austrian laborer with a family history negative for cancer and tuberculosis. Following a head and chest cold twenty months before admission, the patient never fully recovered, but continued to have cough and expectoration. Three months later he went to a diagnostic clinic where an X-ray film showed minimal infiltration radiating from the hilum to the right apex (figure 9). On bed-rest at home he improved to the extent that his cough and expectoration disappeared and he regained the 10 pounds in weight that he had lost. Sputum was negative for tubercle bacilli. Serial roentgenograms, fourteen months and five months before admission, showed no change.

One month before admission the patient developed another chest cold at which time he had heavily blood-streaked sputum. He complained of cough and expectoration and fatigue and, although his appetite was good, he had lost 11 pounds. An X-ray film in the clinic showed increased disease in the right upper lobe, and sanatorium care was advised.

On admission he weighed only 124 pounds. His best previous weight had been 160. A roentgenogram of the chest showed moderate infiltration on the right to the level of the seventh vertebral spine, with a suspicious 3 cm. cavity at the level of the sixth vertebral spine. On the left there were two small calcific nodules at the level of the first and second anterior ribs.

During the patient's first month of residence 2 sputum specimens were negative for tubercle bacilli by direct smear and one was negative by concentration. Two acid-fast bacilli were found in one other concentrated sputum specimen. Hemoglobin was 13.0 g. (84 per cent). Red blood cells were 4,000,000. White blood cells numbered 12,000, with 74 per cent polymorphonuclear cells.

The admission diagnosis was moderately advanced pulmonary tuberculosis. On bed-rest his temperature ranged to 99.2°F. until the third week in the sanatorium when it rose to 101 to 102°F. for ten days. Sputum became blood-tinged, and he developed wheezing over the right chest for the first time. A roentgenogram at that time (figure 10) revealed a 5 cm. cavity with a fluid level in the posterior portion of the right upper lobe. The patient coughed up frank creamy pus and, following this, an X-ray film taken two months after admission showed disappearance of the fluid level. It was felt that the right upper lobe bronchus was intermittently blocked. During the next two months the cavity alternately became larger, smaller and then larger again and the fluid level reappeared.

During the third month of residence he had an hemoptysis.

In the meanwhile, after the single positive sputum, numerous concentrated specimens

were all negative for tubercle bacilli. The possibility of infected pulmonary cyst or carcinoma of the bronchus was considered, and bronchoscopy was done in the third month of residence. There was marked bulging of the antero-medial wall of the right main bronchus, as if from external pressure, and a grayish-white lesion was seen projecting just proximal to the opening of the right upper lobe bronchus. A biopsy from this region revealed squamous cell carcinoma of the bronchus.

On postural drainage the patient was able to keep his cavity dry and his temperature remained essentially normal. He continued to have heavily streaked sputum daily and developed clubbing of the fingers while in the sanatorium. Because of the gross involvement of the right main bronchus and evidence of mediastinal metastases, operation was deemed inadvisable and he was discharged to his home after four months in the sanatorium. The discharge diagnosis was: squamous cell carcinoma of the bronchus; secondary lung abscess, right upper lobe; pulmonary tuberculosis.

Out-patient clinic (seven months later). The patient had continued to lose weight and strength, although a new X-ray film showed no essential change. Death occurred at home just nine days later. Autopsy was not performed.

*T.D.*: A 56 year old male cook. The patient's mother died of cancer of the throat. There was no family history of tuberculosis. The patient claims to have had a "cigarette cough" of fifteen years' duration. Six months before admission he noticed fatigue, weakness, night sweats and loss of 30 pounds in weight. Four months before admission his sputum began to show streaks of blood on frequent occasions. One month before admission he entered a Veterans' Hospital. There, pulmonary tuberculosis was diagnosed on X-ray examination and positive sputum. Chest pain was present along the right border of the sternum, below the level of the third rib. He showed no improvement and was transferred to Laurel Heights.

On admission his general condition was very poor. Temperature ranged to 100°F. The patient was dyspneic and cyanotic, even at rest. He had no adenopathy. X-ray examination of the chest (figure 11) showed irregular mottled and calcific densities in both upper lobes. At the right base, medially, was an ill-defined circumscribed density. A homogeneous shadow obscured the right costo-phrenic angle. Compared with films taken one month before admission there had been no significant change.

Two direct smears of sputum revealed tubercle bacilli. Hemoglobin was 14.0 g. (91 per cent). Red blood cells were 3.95 millions. White blood cells numbered 9,400, with 82 per cent polymorphonuclear cells.

Although the patient was thought to have tuberculosis involving both upper lobes, the dense lesion at the right base suggested tumor at the time of admission. Pleural fluid aspirated from the right thorax was yellow and cloudy, but not blood-tinged. A cell-block of this fluid contained many tumor cells.

The patient's course was rapidly downhill, with severe cough and expectoration and dyspnea. Death occurred on the twenty-second hospital day.

Tissue obtained postmortem by needle revealed epidermoid cell carcinoma of the lung, with involvement of the pleura and metastasis to the liver.

*W.C.*: A 72 year old sandpaper mill employee. His family history was negative for tuberculosis and cancer. For twenty-five years this man had worked in a sandpaper mill where he was exposed to an unknown amount of sand-dust.

The patient had had considerable cough and expectoration for many years. Twelve years before admission he began to experience dyspnea and cyanosis on exertion. His cough increased and he was troubled by pain under the lower ribs anteriorly on the right.

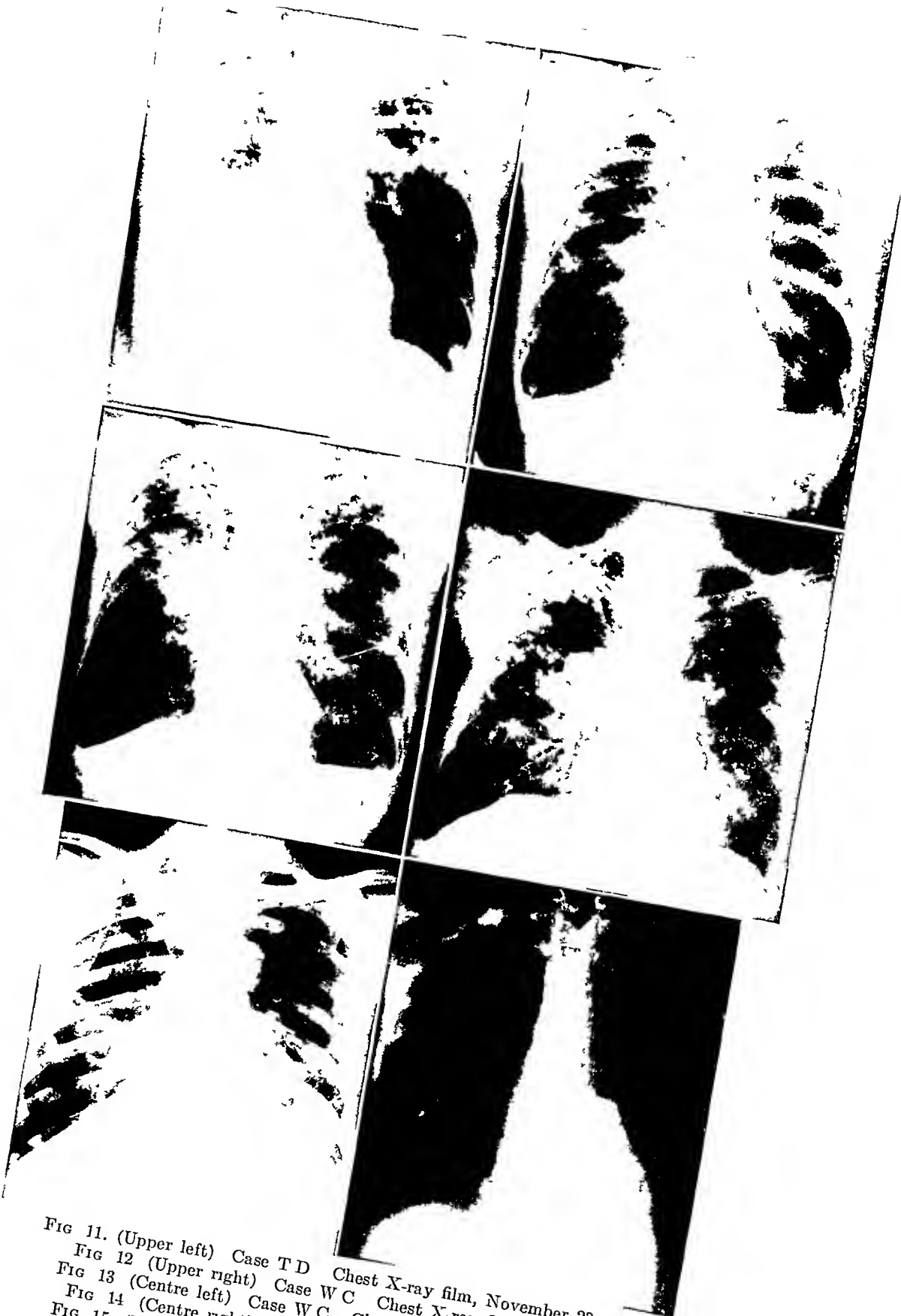


Fig 11. (Upper left) Case T D Chest X-ray film, November 23, 1945  
 Fig 12 (Upper right) Case W C Chest X-ray film, May, 1943  
 Fig 13 (Centre left) Case W C Chest X-ray film, June 14, 1945  
 Fig 14 (Centre right) Case J S Chest X-ray film, July 2, 1945  
 Fig 15. (Lower left) Case W P Chest X-ray film, April 25, 1946  
 Fig 16 (Lower right) Case W.P. Laminagram, May 27, 1946

Six years before admission he entered a local hospital because of his symptoms. At that time an X-ray film of his chest showed only slight diffuse fibrosis throughout both lungs. He was discharged after four days with a diagnosis of pneumoconiosis, chronic bronchitis and emphysema.

At home his symptoms gradually became more severe, so that fifteen months before admission he entered a medical centre. A chest roentgenogram at that time (figure 12) was interpreted as showing minimal pulmonary fibrosis scattered in the right upper lobe, pulmonary infiltration in the right perihilar region and bilateral emphysema. Cardiac silhouette and contour of the aorta appeared normal.

During the following year his dyspnea and the pain under the right costal margin increased. Tubercle bacilli were found in his sputum, and one month later he was admitted to the Undercliff Sanatorium.

At the time of admission his general condition was poor. He weighed only 108 pounds, having lost an unknown amount of weight. He was dyspneic even at rest, especially so at night. Cough was severe and productive. The right pupil was smaller than the left and both reacted sluggishly to light. Babinski reflexes were absent on both sides. He had no adenopathy. Blood pressure was 170/100. The liver was palpable three fingers-breadth below the right costal margin and was slightly tender.

An X-ray film of the chest showed scattered mottled and linear densities to the level of the fourth rib and ninth vertebral spine on the right, with several areas of rarefaction in the apex and midlung. There was an irregular density in the right perihilar region. No infiltration was present in the left lung. Marked emphysema was evident at both bases, with flattening and fixation of the diaphragms. There was widening of the ascending arch of the aorta. Heart was not enlarged.

Repeated concentrated sputum specimens revealed tubercle bacilli. Red blood cells were 3.86 millions. Hemoglobin was 82 per cent. White blood cells numbered 7,500, with 75 per cent polymorphonuclear cells. Mazzini and complement fixation tests for syphilis were positive.

Because of some difficulty in swallowing and repeated emeses, the esophagus was examined with a barium meal. This demonstrated marked constriction of the esophagus in its lower third, with slight dilatation above the constricted area. The possibility of primary cancer of the esophagus was considered.

On account of his age and poor general condition, the patient was subjected to no further diagnostic procedures and was treated symptomatically. His clinical course was slowly downhill, with severe cough and pain under the right ribs. Concentrated specimens of sputum continued to be highly positive for tubercle bacilli. Films taken ten days before death (figure 13) showed marked increase of the infiltration in the right upper lobe, where a 5 cm. cavity had developed in the apex. The perihilar infiltration on the right had also increased and there was new infiltration in the left upper lobe as far down as the sixth vertebral spine. The aortic dilatation was unchanged.

The patient became increasingly weaker and dyspneic and continued to lose weight. Death occurred eight months after admission. An autopsy was performed.

*Autopsy:* A gray, firm tumor mass, 0.5 cm. in diameter, penetrated the lateral and posterior walls of the right main bronchus. It was continuous with tumor masses that occluded completely the right upper lobe bronchus and invaded the outer wall of the esophagus. A 5-cm. cavity, lined by a firm, thick fibrous wall, occupied the posterior segment of the right upper lobe. The remaining areas of the right upper lobe and the right lower lobe showed numerous caseous tubercles. Strands of fibrous connective tissue were scattered in the parenchyma.

The tumor was an epidermoid carcinoma which invaded the right hilar lymph nodes and the longitudinal muscle layer of the esophagus.

A moderate number of small caseous tubercles were seen beneath the pleura and in the parenchyma of the left lung. Several small foci of pneumonia were noted in the left lower lobe.

There was syphilitic mesaortitis, with diffuse widening of the ascending aorta. No evidence of silicosis was found.

*J.S.:* A 62 year old tobacco worker who did not know which diseases might have occurred in his family. The present illness began with an unproductive cough during the two or three years preceding admission. Four months before admission he was troubled by weakness. The weakness increased and he entered a local hospital one month before admission. There he expectorated a small amount of blood. Chest X-ray films were interpreted as showing bilateral, chronic fibratic tuberculosis. He was transferred to the Cedarcrest Sanatorium.

On admission his general condition was fair. He had lost about 9 pounds from his average weight of 122. There was no adenopathy. A roentgenogram of the chest at the time of admission (figure 14) showed dense mottled infiltration scattered through the right lung field, most marked in the periphery of the right upper lobe, with multiple annular shadows suggesting cavitation. In the right hilum was a dense irregularly circumscribed mass measuring 6 cm. in diameter. In the left upper lobe were two small nodular densities.

Concentrated specimens of sputum were positive for tubercle bacilli. Red blood cells were 4.59 millions. Hemoglobin was 89 per cent. White blood cells numbered 12,500, with 68 per cent polymorphonuclear cells.

On bed-rest the clinical course was slowly downhill. The patient remained afebrile. Cough and expectoration were moderate, with frequently bloody sputum. The sputum continued to show many tubercle bacilli. Pain in the region of the mediastinum and referred to the right shoulder was a constant complaint. Over a period of six months, serial X-ray films of the chest showed progressive and rather rapid increase in the size of the mass in the right hilum. Death occurred eight months after admission. An autopsy was performed.

*Autopsy:* Many small tubercles were present in the apex of the right upper lobe. A 2 cm. cavity with a caseous wall was noted in the subapical region.

A gray, lobulated tumor mass, 8 cm. in diameter, occupying the lower posterior third of the right upper lobe, had replaced entirely the parenchyma of the middle lobe and extended into the right lower lobe. The pulmonary parenchyma adjacent to the tumor was compressed and atelectatic. A crescent-shaped cavity, lined by necrotic tissue, was found at the periphery of the tumor, while its central portion had excavated and the resulting cavity was filled by a blood clot. Numerous small abscesses containing pus-like material were found in the lower segment of the lower lobe. Two of the hilar lymph nodes were invaded by tumor. The primary site of the tumor could not be established. It was an epidermoid carcinoma.

Scattered small groups of proliferative tubercles were present in the left lung. An egg-sized metastasis had replaced the right adrenal.

*W.P.:* A 54 year old colored laborer. His family history was negative for tuberculosis and cancer. This man previously had been a patient for six months in the Laurel Heights Sanatorium. At that time he had minimal pulmonary tuberculosis involving the right



upper lobe and there was no evidence of cancer. After leaving the Sanatorium his living habits were irregular. Two years later his sputum became positive for tubercle bacilli and he entered another sanatorium where he again arrested his tuberculosis on bed-rest after eight months. Returning to work he felt unwell, with blood-streaked sputum, dyspnea on exertion, chronic cough, loss of weight and stabbing pain in the left lower chest. He returned to Laurel Heights four years and three months after his first admission.

Second admission: His general condition was poor. Temperature ranged to 100.4°F. He had no adenopathy or clubbing of the fingers. Sputum was highly positive for tubercle bacilli on repeated smears and concentrates. Hemoglobin was 12.5 g. (81 per cent). Red blood cells were 3.62 millions. White blood cells numbered 6,600, with 59 per cent polymorphonuclear cells. Urine contained only one white blood cell per high power field.

X-ray films of the chest on readmission showed infiltration and cavitation in the right apex and paravertebral densities at both bases.

Two months after admission interlobar fluid appeared between the right middle and lower lobes. No bacteria or tumor cells could be demonstrated in small amounts of bloody fluid aspirated on two occasions. At this time right pneumothorax was attempted unsuccessfully. The pleurisy was absorbed.

Eleven months after admission serial films (figure 15) showed progression of the basal densities into the peripheral areas of both lower lobes, with apparent cavitation in these areas. This took place during a period when the patient was afebrile and was maintaining his weight. Malignancy was again suspected and this time the diagnosis was confirmed by the finding of tumor cells in a cell block of sputum. Bronchoscopy revealed no evidence of tumor.

Laminagrams (figure 16) demonstrated clearly an irregular mass containing multiple ragged-walled cavities behind the heart in the left lung. In addition the tuberculous cavity in the right apex was sharply outlined. Needle puncture of the left lower lobe yielded bloody pus and tissue which showed microscopically epidermoid cell carcinoma.

In the fourteenth month of residence the patient was afebrile but was slowly losing weight and becoming weaker. Sputum continued to contain large numbers of tubercle bacilli.

#### DISCUSSION

The most pertinent clinical, laboratory and roentgenological findings in these cases are summarized in tables 1 and 2. Only in case *H.D.* did the diagnosis of tuberculosis present a problem. In all the others the presence of pulmonary tuberculosis was readily apparent and was promptly confirmed by the finding of tubercle bacilli in sputum soon after admission.

A survey of tables 1 and 2 makes it apparent that detection of cancer in these cases is so difficult because reasons for suspecting a second disease are ostensibly meager. Such listed symptoms as bloody sputum, cough, expectoration, pain in the chest, loss of weight, etc., and such findings as secondary anemia, and X-ray densities of the most heterogeneous character are so common in tuberculosis that they are likely to be taken as a matter of course. Evidences of cancer tend, therefore, to be obscured by the tuberculosis. In every one of our cases, however, there were features, either upon admission or developing later, which led to the suspicion of cancer, and from this to a specific and detailed search for the disease.

It appears worth while, therefore, to discuss these features as they occurred in the 7 cases observed clinically at Laurel Heights by the authors.

TABLE 1  
*Summary of clinical findings*

PATIENT	HISTORY					SIGNS AND SYMPTOMS									
	Sex	Age	Tuberculosis in family	Cancer in family	Exposure to silica dust	Pain	Dyspnea	Bloody sputum	Wheezing	Loss of weight	Cough	Weakness, fatigue	Clubbing of fingers	Anorexia	Swallowing difficulty
S. B.	M	57	0	0	0	0	0	+	+	+	+	+	+	0	0
W. C.	M	72	0	0	+	+	+	0	0	+	+	+	0	+	+
H. D.	M	55	0	0	+	+	+	+	0	+	+	+	+	+	0
T. D.	M	56	0	+	0	+	+	+	+	+	+	+	0	+	0
A. M.	M	64	0	0	+	0	+	+	0	+	+	+	+	+	0
J. M.	M	51	+	0	+	+	0	+	0	+	+	+	0	+	0
R. P.	M	63	0	0	0	0	+	+	+	+	+	+	0	0	0
W. P.	M	54	0	0	0	+	+	+	+	+	+	+	0	0	0
J. S.	M	62	?	?	0	+	0	+	0	+	+	+	0	0	0

TABLE 2  
*Summary of laboratory, x-ray and diagnostic findings*

PATIENT	LABORATORY						X-RAY						DIAGNOSIS CONFIRMED BY					
	Tubercle bacilli in sputum			W.B.C. (X 1000)	R.B.C. (X 1,000,000)	Hemoglobin (%)	Mass	Hilar infiltration	Hilar or mediastinal nodes	Bronchial obstruction	Atelectasis or shrinkage	Cavity	Bronchial biopsy	Bronchial bulging	Needle biopsy	Cell-block sputum	Cell-block pleural fluid	Autopsy
	Smear	Concentrated	Guinea pig															
S. B.	0	+		12	4.00	84		+		+		+	+	+				
W. C.		+		7.5	3.86	82		+				+	NB					+
H. D.	0	0	+	11.8	3.98	84	+		+	+	+	+		+				+
T. D.	+			9.4	3.95	91	+						NB		+		+	
A. M.	+			24.4	4.46	81	+		+	+	+		NB					+
J. M.	+	+		10.4	4.21	94		+	+		+	+	+			+		
R. P.	0	+	+	7.8	3.78	78				+	+	+	+	+				
W. P.	+	+		6.6	3.62	81	+	+			+	+			+	+		
J. S.		+		12.5	4.59	89	+	+	+			+	NB					+

N.B. = Not bronchoscoped.

*Case A.M.:* The X-ray and clinical findings immediately pointed to an atelectasis or obstructive pneumonitis involving the right lower and middle lobes. It was felt that major bronchial obstruction was most likely due either to tuberculous bronchostenosis or to tumor. Laminagrams demonstrated obstruction by what appeared to be a solid mass, and a presumptive diagnosis of cancer was

made. This diagnosis was confirmed by biopsy of the metastatic lesion in the right radius. Bronchoscopy was not performed because the patient's condition was almost terminal, and further confirmation at autopsy was anticipated.

*Case J.M.:* Diagnosis in this patient resulted directly from a clinical *tour de force* on the part of his attending physician. His clinical course and the X-ray appearance and behavior of his disease were not regarded as atypical of the established tuberculosis until, on routine rounds, it was noted that his sputum had an unusual "meaty" appearance. A sputum specimen was then collected in 10 per cent formalin and submitted for cytological study. After review of the case it was apparent that, with a generally favorable clinical trend and with disappearance of tubercle bacilli from the sputum, there was, nevertheless, progressive roentgenographic increase in the pulmonary densities in the right upper lobe. Moreover, blood-streaked sputum was recurrent, and pain in the chest was increasingly prominent. The diagnosis of coexisting cancer was established by the finding of tumor cells in the sputum cell block. This diagnosis was confirmed by bronchoscopic biopsy.

*Case R.P.:* Cancer was first suspected in this case when, in spite of slight clinical improvement, routine X-ray reexamination showed complete atelectasis of the right upper lobe. Tuberculous bronchostenosis was regarded as the other major possibility. Bronchoscopic evidence of a mass impinging upon the trachea was clearly in favor of cancer, though confirmation by biopsy was not obtained until another bronchoscopy was performed several months later.

*Case H.D.:* In this case opinion as to diagnosis vacillated for a long time between tuberculosis and cancer. In retrospect, it must be admitted that evidence for cancer was far stronger than for tuberculosis, at least until very late. Not only were the symptoms out of proportion to an uncomplicated tuberculous lesion of the character and extent seen by X-ray at the time of his first admission, but the findings at the first bronchoscopy were adequate to justify a presumptive diagnosis of cancer. Had laminagraphy been available at that time, the presumption might have been even stronger; for laminagrams, made ten months later, showed that the large mass surrounding and constricting the right main bronchus was clearly delineated. Although tuberculosis was strongly suspected from the beginning, proof of its existence by guinea pig inoculation of sputum was not complete until after death. Both diseases were demonstrated by autopsy.

*Case S.B.:* Cancer soon became a rather obvious possibility in this case. There was unequivocal evidence, both clinically and roentgenologically, of narrowing and intermittent occlusion of either the right upper lobe bronchus or of a major branch. Moreover the progressive symptoms and X-ray behavior of the disease, including obvious cavitation, were scarcely compatible with an uncomplicated tuberculosis productive of only one positive sputum among several good specimens examined. Diagnosis of carcinoma was readily established bronchoscopically.

*Case T.D.:* This patient's condition was terminal on admission. His condition could reasonably have been accounted for by the extensive active tuberculosis. The mass in the right lower lobe seen on X-ray films was, however, atypical for

tuberculosis and suggested cancer. Because of the clinical status, bronchoscopy was not feasible. Diagnosis of cancer was confirmed by finding cancer cells in a cell block of pleural fluid before death. Since autopsy was refused, multiple post mortem specimens of tissue were obtained by needle. These clearly demonstrated bronchogenic cancer and, by chance, also a liver metastasis.

*Case W.P.:* At the time of this patient's first admission, the clinical and X-ray pictures were those of minimal right upper lobe tuberculosis. His second admission took place four and a quarter years later. Then the character of the basal densities was questioned but these were accepted as being spreads of tuberculosis. Two months after admission evidence of cancer of the lung was unsuccessfully sought when the bloody pleural effusion aroused suspicion. Progression according to X-ray examination of the basal lesions that was not clinically manifested led to the search for tumor cells in the sputum.

It is quite probable that this patient had only pulmonary tuberculosis at the time of his first admission. This case emphasizes the difficulty of recognizing cancer of the lung appearing in the presence of a previously observed pulmonary tuberculosis. Diagnosis of cancer was made by finding tumor cells in a cell block of the sputum and by needle puncture. Bronchoscopy was of no assistance in this case.

Neurological changes were not observed in any of the patients.

#### CONCLUSIONS

To the extent that we can judge from this group of 9 patients with pulmonary tuberculosis and bronchogenic carcinoma, the following conclusions appear to be justified:

1. All cases recognized by us were men and all were over 50 years of age.
2. Four cases gave a history of significant exposure to silica dust.
3. In tuberculous as in nontuberculous patients, suspicion of cancer rests first upon the correlation of clinical and roentgenological findings. Tuberculosis alone is capable of producing all the prominent symptoms encountered in these patients. Hence, history, symptoms and clinical findings generally contributed far less to the initial suspicion of cancer than did X-ray examination. Clinical features were of great importance, however, when they failed to conform to the pattern usually expected to result from uncomplicated tuberculous lesions of the extent and behavior shown by X-ray.
4. While there are individual exceptions, notably among Negroes, the principal lesions of adult reinfection pulmonary tuberculosis occur typically in the peripheral lung zones, not near the hilum. Tuberculous lesions projected into the hilum in single posterior-anterior roentgenograms usually occupy the apex of a lower lobe. Hence, when posterior-anterior and lateral films indicate true hilar infiltration, cancer should be suspected—the more strongly if a mass is suggested or if hilar lymph nodes are involved. Such findings can often be demonstrated far more clearly in good laminagrams than in plain roentgenograms.
5. The finding, by conventional films, of evidences of major bronchial obstruction or of a relatively circumscribed solid mass deserves credit for initiating more

definite diagnostic procedures in the majority of our cases. While the former may be caused by tuberculous bronchostenosis or by pressure of enlarged tuberculous lymph nodes, and the latter by tuberculoma, the need for further investigation is apparent, especially in older patients.

6. The diagnostic procedures available for confirmation of cancer are well known. These are bronchoscopy, biopsy of suspected metastatic lesions, cell block of formalinized sputum, cell block of formalinized pleural fluid sediment, needle biopsy and surgical exploration. To be of diagnostic value, cell blocks of pleural fluid sediment require prolonged search of many sections.

None of the cases reported here was deemed operable at the time of diagnosis. Hence, the advantage of having the diagnoses made before death rather than at autopsy alone was slight indeed from the therapeutic point of view. There were practical advantages, however, in that more intelligent prognosis and management were made possible.

Since pulmonary resection is now feasible in many cases of tuberculosis, the practical desirability of much earlier diagnosis of coexisting cancer is apparent. It is, perhaps, not too much to hope that diagnosis of cancer in an operative stage may occasionally be accomplished in spite of the added difficulty which exists when tuberculosis is also present.

#### SUMMARY

1. Nine cases of coexisting pulmonary tuberculosis and bronchogenic carcinoma are reported, with autopsy findings in 4.

2. Obstacles to the diagnosis, especially to early diagnosis, of carcinoma in the presence of known tuberculosis are emphasized. The greatest obstacle is failure to suspect a second major disease.

3. The diagnosis of pulmonary tuberculosis was readily and promptly apparent in all cases except one. Clinical, laboratory and roentgenological findings leading to the more difficult diagnosis of cancer are discussed.

#### SUMARIO

1. Comunícanse nueve casos de tuberculosis pulmonar y carcinoma broncogénico coexistentes, con los hallazgos autópsicos en 4.

2. Hácense resaltar los obstáculos con que tropieza el diagnóstico, en particular temprano, del carcinoma cuando se conoce la presencia de tuberculosis, siendo el principal el no sospecharse la existencia de otra enfermedad de mayor importancia.

3. El diagnóstico de la tuberculosis pulmonar fué rápido y manifiesto en todos los casos, menos uno. Discútense los hallazgos clínicos, radiológicos y de laboratorio que conducen al diagnóstico, más difícil, del cáncer.

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# CYTOLOGY OF BRONCHIAL SECRETIONS<sup>1</sup>

## A Diagnostic Aid in the Diagnosis of Pulmonary Tuberculosis

PETER A. HERBUT AND LOUIS H. CLERF

In the course of our study of bronchial secretions for cancerous cells (1) we were at first baffled by the presence in some cases of small or large clusters of unusual epithelial cells. Sometimes they were quite regular but at other times they were rather bizarre and, except for the fact that they always contained cilia, they often bore a superficial resemblance to cells found in a low grade epidermoid bronchogenic carcinoma. When the cases were being brought to a final conclusion it became apparent that those exhibiting many such collections were from patients with pulmonary tuberculosis and that secretions from patients with other diseases, and particularly chronic tracheo-bronchitis, bronchiectasis and pulmonary abscess, usually presented a complete absence or at the most only one or two clusters of somewhat similar cells. This observation has proved to be of considerable practical significance; for by this method we have on several occasions been able to make a presumptive diagnosis of pulmonary tuberculosis six weeks before a culture of tubercle bacilli could be obtained. By the same token we have spared those patients, whose tuberculous lesion was atypical and confused with primary bronchogenic carcinoma, an exploratory thoracotomy.

In a series of 210 examinations of bronchial secretions there were 57 cases of proved bronchogenic carcinoma, 47 of which revealed cancer cells in the bronchoscopically aspirated material. In the same series there were 13 cases considered clinically as carcinoma in which a cytological diagnosis of tuberculosis was made and in which tubercle bacilli were later isolated. There was only one case in which a positive diagnosis of tuberculosis was made and in which this disease has not yet been substantiated.

In this paper we wish (1) to refer briefly to the technique employed in preparing the smears and (2) to present some of the cases in which this procedure proved of value.

### MATERIAL AND METHOD

The procedure used in obtaining the secretions and preparing the smears is exactly the same as that employed in the cytological study of secretions for bronchogenic carcinoma (1). At an ordinary bronchoscopy, secretions are secured in a regular or special collector (attached directly to the aspirator) from the bronchus or bronchi draining the suspected area. If the amount of material secured is scanty all is smeared, but if it is abundant it is first poured into a flat transparent dish and those portions streaked with blood or containing small grey particles are transferred to clean glass slides. Smears are made by the crush method using another slide and the material is spread to a thickness of an ordinary blood smear. While still wet the slides are dropped into equal parts of

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95 per cent alcohol and ether where they are fixed for thirty minutes after which they are stained by the Papanicolaou technique (2). Every portion of every slide is systematically examined first with 80  $\times$  and then with 400  $\times$  magnification, using subdued light.

#### REPORT OF CASES

*Case 1:* A white woman, 53 years of age, had pain in the right chest and fever for four weeks. Physical examination was essentially normal. There was slight fever. Roentgenograms of the chest revealed a shadow in the lateral portion of the right side of the chest that was interpreted as basilar or interlobar in position and suggested carcinoma (figures 1A and B). Repeated examinations of the sputum for tubercle bacilli were negative. Two bronchoscopic examinations revealed no abnormality in the tracheo-bronchial tree.

About 2 cc. of blood-tinged tenaceous secretions were removed at each bronchoscopic examination. Smears of each of these were essentially the same except that those made from the first specimen were less cellular. Detailed microscopic examination revealed many erythrocytes, very little fibrin and only a slight amount of detritus. There were very few cells of inflammatory origin, consisting of neutrophils, lymphocytes and occasional plasma cells and only scattered mononuclear phagocytes. The latter were at times quite large and exhibited as many as seven eccentrically placed round evenly stained nuclei. Regular ciliated columnar epithelial cells, both single and bunched, were fairly numerous in the second specimen. The most characteristic feature, however, was the presence of many rounded clusters of epithelial cells (figure 2). The number of cells in each cluster varied from 3 or 4 to 50 or 60. They were closely packed so that their borders were not readily discernable. The cytoplasm stained from blue to deep red or purple and often contained vacuoles. In the latter the nuclei were usually pushed peripherally and often assumed crescentic shapes. Otherwise they were round, oval or oblong and although they varied in size they never replaced all or even most of the cytoplasm. They were as a rule heavily but uniformly stained showing no clumping of the nucleoplasm. There was just enough variation in shape, size and staining qualities of the cells to harbor the suspicion that they could have represented sloughed portions of a low-grade squamous cell carcinoma except for the fact that every collection contained cilia. In addition to these packets there were many ballooned and rounded single cells with sharp margins, light bluish stained, often vacuolated cytoplasm and round, oval or crescentic deeply stained nuclei. These cells, too, were always ciliated.

The cytology was, therefore, compatible with tuberculosis but smears from each specimen did not reveal any acid-fast bacilli. A culture of tubercle bacilli, however, was obtained from the second specimen six weeks after inoculation.

*Case 2:* A white man, 63 years of age, had a dry cough for twelve months, hemoptysis for two weeks and pain in the upper portion of the right chest for two days. There was no fever. Physical examination and a roentgenogram of the chest revealed a lesion in the right lung that was considered to be atelectasis of the middle lobe with a possible interlobar collection of fluid (figures 3A and B). This was interpreted as being carcinoma. Bronchoscopic examination disclosed a complete occlusion of the orifice of the bronchus to the middle lobe but it could not be determined whether this was endobronchial or extrabronchial in origin. It was impossible to secure tissue for histological study.

Smears of secretions removed at the time of bronchoscopy disclosed a small amount of debris and fibrin, moderate numbers of neutrophils, a few lymphocytes, fewer plasma



cells and only an occasional mononuclear phagocyte. Single regular appearing columnar cells were present in moderate numbers. Again the most characteristic feature was the presence of numerous rounded islands of dense epithelium that always contained cilia

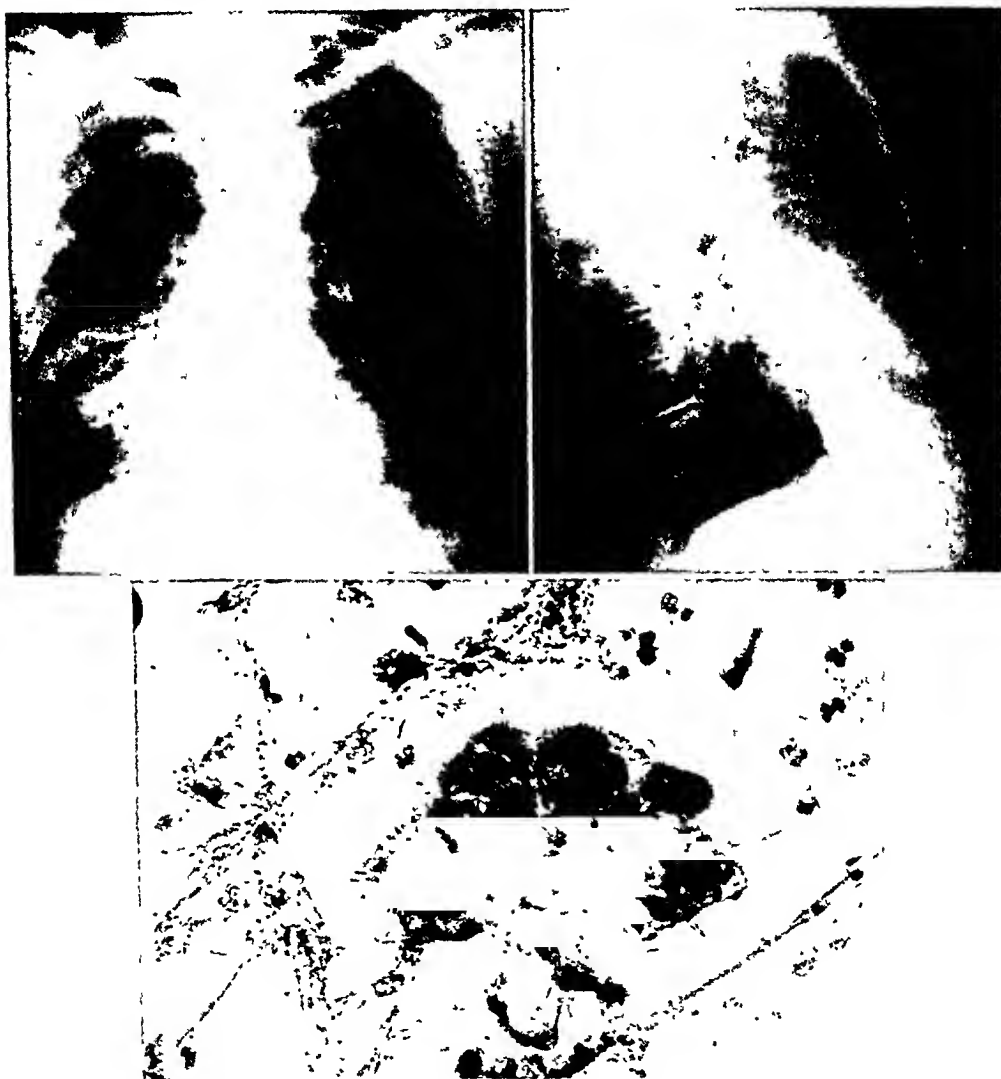


FIGS. 1A (Upper left) and 1B (Upper right). Case 1. Roentgenogram of the chest showing an irregular shadow in the right lung field.

FIG. 2 (Lower). Case 1. Smear of bronchial secretion showing a rounded collection of epithelial cells staining gilia. Papanicolaou stain  $\times 400$ .

(Fig. 2). The cells were large, very round, usually sharp but sometimes irregular in outline, with a very distinct border (Fig. 2). The nuclei were round, oval or elongated, stained dark. There were also poorly represented collections of 2 to 4 cells and 1 to 2 cilia (Fig. 2). The cells were not at all flattened. The cells were

larger, more distinct and the often vacuolated cytoplasm was light gray or green. The nuclei were round or oval and evenly stained but in the vacuolated cells they were crescentic, deeply stained and pushed aside. There were also present large cells with abundant



FIGS. 3A (Upper left) and 3B (Upper right) Case 2. Roentgenogram of the chest showing a shadow in the right lung that was considered to be cancer.

FIG. 4. (Lower) Case 2. Smear of bronchial secretion showing a clump of epithelial cells containing numerous cilia. Papanicolaou stain  $\times 400$ .

cytoplasm and numerous round or oval peripheral nuclei which closely resembled Langhans' giant cells.

A diagnosis of tuberculosis was thus made. Acid-fast bacilli were then demonstrated in smears of the same secretion and a culture subsequently revealed a growth of tubercle bacilli.

*Case 3:* A white man, 73 years of age, had cough, expectoration, pain in the right side of the chest and a loss of 39 pounds in weight over a period of three months. Roentgenograms of the chest revealed anthracosilicosis (the patient was a miner) and in addition a shadow in the upper lobe of the right lung that was considered to be atelectasis caused by a carcinoma. Bronchoscopic examination disclosed no abnormality.

Smears made of secretions removed at bronchoscopy disclosed some debris, fibrin, few neutrophils, scattered plasma cells and an occasional pavement cell. Single regular ciliated columnar epithelial cells were scanty in some fields but numerous in others. Also irregularly distributed were oval or oblong cells with scanty, ill defined, pink cytoplasm



FIG. 5. (Left) Case 3. Smear of bronchial secretion showing a large mass of epithelial cells with cilia along one border. At the top there is a smaller rounded collection of 4 cells that also exhibit cilia. Papanicolaou stain  $\times 400$ .

FIG. 6. (Right) Case 3. Smear of bronchial secretion showing a Langhans' giant cell. The cytoplasm is abundant and pink and the nuclei are uniformly stained and eccentric. Papanicolaou stain  $\times 400$ .

and evenly stained nuclei. These were either single or bunched together in large masses and looked not unlike epithelioid cells seen in histological sections of tuberculous tissue. Rounded clusters of a few or many epithelial cells with cilia were numerous in all smears (figure 5). As in the previous cases the cells varied considerably. Those in greater numbers were closely packed and resembled squamous epithelium, whereas those in fewer numbers were less dense and resembled more columnar and cuboidal cells. The cytoplasm of the former was pink, indistinct and not too abundant, while that of the latter was blue-green or grey, sharply demarcated and often vacuolated. The nuclei in each were round, oval or crescentic and deeply stained. In addition to the above cells there were structures that looked very similar to Langhans' giant cells (figure 6). The cytoplasm was abun-

dant, pink and fairly sharp. Numerous oval, round or oblong, evenly stained, clumped nuclei were eccentrically placed or disposed more or less uniformly about the periphery.

From a study of these smears a diagnosis of pulmonary tuberculosis was made. The remaining secretions which had not yet been destroyed were smeared and stained for acid-fast bacilli but no organisms were found. A culture of the same material, however, six weeks later yielded a growth of tubercle bacilli.

#### COMMENT

Ordinarily there is little difficulty in arriving at a correct diagnosis of pulmonary tuberculosis but sometimes the lesion is so situated and the accompanying signs and symptoms are so atypical that its true nature is completely masked. This is well demonstrated in case 2. The central position of the lesion and the lack of constitutional disturbances made the diagnosis of bronchogenic carcinoma a very good possibility. Tuberculosis, on the other hand, was not suspected until smears of bronchial secretions were examined cytologically following which proper staining of the remaining discarded but not destroyed secretions revealed tubercle bacilli and so sealed the diagnosis. Case 1 is very similar, except that repeated examinations of sputum failed to disclose tubercle bacilli and smears of two bronchoscopically removed secretions likewise failed to reveal the organisms. Because of this the suspicion that the lesion was cancerous rather than tuberculous was entertained more and more until the cytological examination disclosed cells compatible with tuberculosis and, of course, until six weeks later tubercle bacilli were cultured from the secretions. It is in this type of case that cytological study of bronchoscopically removed secretions is of the greatest value for, if the lesion is cancerous, a pneumonectomy should be performed without delay but, if it is tuberculosis, a thoracotomy is ordinarily contraindicated. The examination is also of value in cases similar to our third one when the patient has anthracosilicosis and in addition either apical tuberculosis or cancer and when by bronchoscopic examination one can demonstrate neither lesion.

It must be emphasized, however, that only a presumptive and not a definitive diagnosis of pulmonary tuberculosis can be made from a cytological study of bronchoscopically removed secretions and that the isolation of the tubercle bacillus is the only unequivocal criterion. But this same statement also holds for a morphological diagnosis of tuberculosis from histological sections and yet this method is practiced routinely. In smears there are two elements which arouse a suspicion of pulmonary tuberculosis, namely, (1) the presence of numerous collections (three dozen or more in one slide) of ciliated epithelial cells and (2) the presence of giant cells of the Langhans type. Why should the cytology of bronchial secretions of patients with tuberculosis differ in any way from that in smears of cases with nonspecific tracheobronchitis, bronchiectasis or pulmonary abscess? We can not answer this except to say that many of the latter cases have been examined for comparison and none has shown similar findings. It is apparent that in cases of pulmonary tuberculosis exhibiting this cytology there must be an ulceration of the epithelium of the bronchi before the

tenth branching—the level at which the epithelium becomes ciliated. In the process of ulceration the cells break off in large numbers in clumps or singly and, since they are spontaneously sloughed, their borders are always rounded. This is extremely important for occasionally in cases other than tuberculosis, and as a result of trauma with the bronchoscope, one sees single or groups of ciliated epithelial cells but the outer margins of these are always ragged and rough. Finally, are the large cells with multiple nuclei Langhans giant cells? We believe they are. In the cell illustrated in the photomicrograph the nuclei are arranged in a clump and eccentrically placed rather than uniformly around the periphery as they are usually found in histological sections. This difference can be accounted for by the fact that the cells in smears are crushed, whole cells whereas those in histologic sections are cut across. Furthermore, in case 2, and in other cases not reported here, there were present giant cells with a single row of peripheral nuclei which were identical morphologically with Langhans' giant cells as we know them.

#### SUMMARY

A presumptive diagnosis of pulmonary tuberculosis can be made from a cytological study of smears made of bronchoscopically removed secretions and stained by the Papanicolaou technique. Of importance in the diagnosis is the presence of rounded clusters of ciliated epithelial cells, single ballooned and vacuolated ciliated epithelial cells and giant cells of the Langhans type.

This method is of particular value in differentiating pulmonary tuberculosis from carcinoma in patients in whom the lesions are atypically situated, in whom there is little constitutional disturbance and in whom repeated examination of sputum fails to reveal tubercle bacilli.

#### SUMARIO

Puede formularse un diagnóstico presuntivo de tuberculosis pulmonar por el estudio citológico de los frotos de las secreciones extraídas broncoscópicamente y teñidas con la técnica de Papanicolaou. En el diagnóstico reviste importancia la presencia de racimos redondeados de células epiteliales ciliadas, de células epiteliales ciliadas globosas y vacuoladas aisladas y de células gigantes del tipo de Langhans.

Este método resulta en particular de valor para diferenciar la tuberculosis pulmonar, del carcinoma en los enfermos que muestran localización atípica, en los que hay pocos trastornos orgánicos y en los que exámenes repetidos del esputo no revelan bacilos tuberculosos.

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## PNEUMOTHORAX FLUID<sup>1,2</sup>

### Its Management by Systematic Aspiration

KIRBY S. HOWLETT, JR. AND HAROLD L. EHRENKRANTZ

In spite of modern case selection and modern pneumothorax management, the pleural fluid problem still plagues us. Differences of opinion still exist as to the best modes of attack. Comments will be confined here to management of pure tuberculous exudates. Management of mixed tuberculous and pyogenic empyema will not be discussed.

At Laurel Heights significant pure tuberculous exudates, purulent and non-purulent, are aspirated regularly. This policy does not embrace therapeutic aspiration of minimal and insignificant accumulations of fluid in the costophrenic sulcus; but only these are excepted.

Aspiration is started early and is repeated frequently enough to prevent the accumulation of more than a small amount of fluid at any time. Even daily aspiration may, exceptionally, be required. Once or twice a week is usually adequate. The principle followed is simply that frequent small aspirations are vastly preferable to less frequent larger ones.

Regular aspirations are continued until pleural fluid disappears or until obliteration of the pleural space is complete. This may involve only one or two aspirations, or well over a hundred, depending entirely on the case. Care is taken to choose an aspiration site so located, and to place the patient in such a position, that each aspiration evacuates all the fluid present—or as nearly all as is technically possible. If collapse by pneumothorax is to be tentatively maintained, air is replaced through the thoracocentesis needle in amounts required to maintain the type of pulmonary collapse desired.

If pneumothorax is to be abandoned, no air whatsoever is replaced unless troublesome symptoms due to high negative intrapleural pressure demand it. Such symptoms are common when large quantities of fluid are removed without air replacement at a single session, but occur rarely when frequent small aspirations are employed. As obliteration of the space proceeds, frequent aspiration is continued to the very end, with change of the site as the diminishing size of the residual fluid pocket requires. When a lung resists expansion, the interval between aspirations is kept short, even when the amount of fluid obtainable at each session becomes quite small. Otherwise, formation of *ex vacuo* fluid may keep pace with aspiration and prevent complete obliteration of the pleural space. Air is not replaced to adjust intrapleural pressure to some arbitrary value. Intrapleural pressure in these cases commonly becomes far too highly negative to be measured with the usual pneumothorax manometer and may safely be ignored in the absence of symptoms.

<sup>1</sup> From the Laurel Heights State Tuberculosis Sanatorium, Shelton, Connecticut.

<sup>2</sup> Presented, in condensed form, before the Medical Section at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 11, 1946;

The program just outlined is neither laborious nor difficult. Pleural irrigations, detergent solutions and so-called pleural antiseptics are not employed. Elaborate apparatus and fancy technique are quite unnecessary. All one needs is a 50 cc. syringe, a tight stop cock and a needle long enough to reach a particular patient's fluid and of large enough gauge to get it out. We provide needles of several different lengths and gauges—say one and one-half, two and three inches long; and 15 and 13 gauge. A suitable needle is always available for any patient. A long needle can be chosen when the patient's thoracic wall (including parietal pleura) is thick; a large gauge needle can be chosen when it is needed to permit the free flow of pus or of fluid containing fibrin particles. This may appear obvious, but it is our observation that one of the commonest causes of difficult or unsuccessful thoracocentesis is a needle which is either of too small gauge or too short.

The aspiration program followed at Laurel Heights is neither new nor original. In recent years, studies by Cournand and Richards (1), Pinner (2) and others

TABLE 1  
*Comparative results of treatment—previous and recent programs*

	GROUP I 1933-1935	GROUP II 1942-1944
Pneumothorax	61	100
Significant fluid	33	34
Empyema	7	7
Frank bronchopleural fistula	3	0
Average duration of fluid	15 months	6 months
Fever over 100° accompanying fluid	21	18
Average duration of fever > 100° F.	60 days	24 days
Fluid eliminated	18	31

have permitted a better understanding of certain aspects of the problem—notably the harmful effect of pleurisy upon pulmonary function. Hence pneumothorax with fluid is promptly abandoned far more commonly now than formerly, and the whole aspiration program has been intensified. Present practice in our clinic represents, however, merely the logical evolution of policy advocated by Nalbant (3) more than fifteen years ago, and again emphasized by Barnwell (4) in 1937. Similar practice is routine in scores of clinics to-day.

Yet practice over the country is still far from uniform. In proportion to the total number of pneumothorax patients treated in 1943, and 1944, aspiration was performed at Laurel Heights more than eighteen times as frequently as in three other sanatoria in our section. It seems worth while, then, to renew discussion of an old topic.

Table 1 shows certain data in two groups of pneumothorax cases. The first group (1933 to 1935) received treatment at a time when our aspiration program was distinctly inadequate by contrast to the second group (1942 to 1944), when the program was much the same as it is to day. Each group is composed of all

cases with pneumothorax induced in our own clinic within each two-year period and maintained longer than two months. We have recorded what happened within an observation period of from two to four years. Fluid recorded in the table means fluid of some significance—that is an amount more than filling the costophrenic sulcus.

The numbers presented in table 1 are small and statistical differences between the two groups are of questionable significance. In group II, for example, the incidence of fluid and of empyema is not strikingly less than in group I, in spite of far more judicious case selection in the 1942 to 1944 period. It should be stated in this connection that it is still the policy in our clinic to administer pneumothorax to selected patients with active exudative or even pneumonic disease. The recognized risk of pleural complications in these cases is deliberately accepted when it is felt that the risk of progressive pulmonary disease is a still greater threat.

Obviously systematic thoracocentesis cannot prevent pleural exudates. Our belief in its superiority over infrequent and haphazard thoracocentesis as a means of managing them, once they occur, is based principally upon our own clinical experience with both methods. This belief does receive some support, however, from the figures in table 1 which pertain to duration of fluid, duration of fever and the relative frequency with which fluid was completely eliminated in the two groups. The most pertinent figures in table 1 appear in the bottom line. After one or more episodes, fluid finally disappeared without further recurrence in only a little over half of the first group and in all but 3 of the second group. Two of these 3 failures were patients who died of pulmonary disease within two months after fluid appeared. Hence there was scarcely time for fluid to be successfully treated. Only one patient in group II still has persistent fluid (case 4 below).

In the 31 successful cases of group II, fluid was eliminated by aspiration and maintenance of pneumothorax in 9, by aspiration, expansion of lung and obliteration of the pleural space in 17, by aspiration and thoracoplasty in 5.

While these figures are of interest, our major reasons for advocating systematic thoracocentesis are clinical, not statistical. These reasons can be best explained by commenting upon some of the common objections to such a program and by discussing the rationale for the program in connection with a few illustrative cases.

Some men still believe that frequent thoracocentesis increases the risk of secondary infection. This is entirely contrary to our experience. Two empyemata in group I and one empyema in group II were mixed tuberculous and pyogenic. The first 2 followed broncho-pleural fistula, the third followed a pneumothorax refill in another clinic. Not one followed thoracocentesis.

Another objection sometimes raised to frequent thoracocentesis is that needle track infections are more likely to occur. Large gauge needles are feared for the same reason. To be sure, a needle track infection cannot occur without a needle track. Yet no one would conclude from this that thoracocentesis should not be performed at all; for to withhold thoracocentesis completely would obviously



be to court far more serious consequences (see cases 5 and 6). It is our belief that the great majority of tuberculous needle track infections arise not from the deposit of bacilli along the track as the needle is withdrawn, but rather from reflux of heavily infected fluid into the pleural end of the temporarily vulnerable needle track after aspiration is completed. This belief is supported by our experience that significant needle track infections occur most often in patients who have heavily infected tuberculous pus which is technically hard or impossible to evacuate completely.

The prevention and treatment of needle track infections in our clinic consists principally of keeping pleural exudate at a minimum and maintaining a high negative intrapleural pressure. Both objectives are accomplished by frequent complete evacuation of fluid without air replacement. In addition, when heavily infected exudate is aspirated, a pressure dressing of sponge rubber strapped tightly with adhesive over sterile gauze is applied after aspiration and cough is temporarily suppressed. These measures minimize the opportunity for residual fluid to be forced into the needle track following thoracocentesis. By the same reasoning, a large-gauge needle will reduce rather than increase the risk of tuberculous needle track infection if it permits the free and complete evacuation of exudate which is either too thick or too full of particulate material to flow freely through a smaller needle.

In our 1942 to 1944 series of cases only one tuberculous needle track infection occurred (see case 4 below). This healed completely when a residual tuberculous empyema pocket was found and was aspirated regularly. Experience with this group, then, is strictly in line with the beliefs advanced in the two previous paragraphs.

By and large, the worst feature of pleurisy complicating pneumothorax is pleural thickening. This impairs pulmonary function and prevents easy reëxpansion of the lung. Both effects are especially bad if fluid is allowed to accumulate in quantity. Then hydrostatic pressure is considerable, and produces excessive collapse of the lower lobe, where collapse is usually least needed. This makes both loss of function and the problem of reëxpansion much greater than they need be.

Frequent aspiration cannot *prevent* pleural thickening. But it can keep fibrinous exudate at a minimum and speed up obliteration of the pleural space. Thus it can minimize pleural thickening and its harmful effects.

#### CASE REPORTS

Case 1: A. B. This patient had a left pneumothorax induced in 1934 for disease confined to the left upper lobe. A selective pneumothorax was obtained with minimal collapse of the uninvolved lower lobe. When fluid occurred and was allowed to accumulate, the

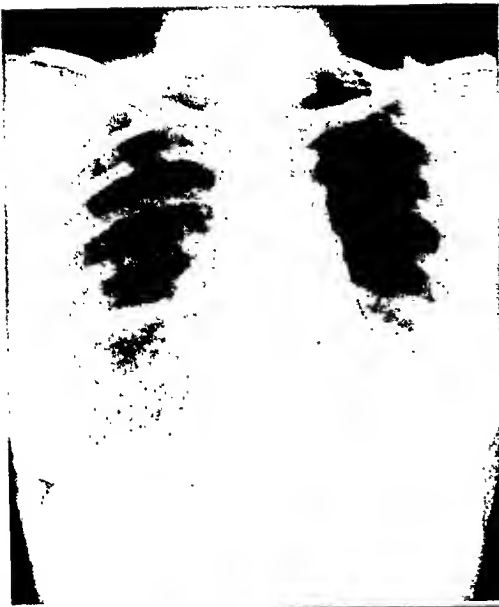
FIG. 1A. (Upper left) Case 2. July 4, 1945.

FIG. 1B. (Upper right) Case 2. March 11, 1946.

FIG. 2A. (Centre left) Case 3. February 2, 1943.

FIG. 2B. (Centre right) Case 3. July 12, 1944.

FIG. 2C. (Lower) Case 3. June 7, 1945.



Figs. 1A to 2C

lower lobe was completely collapsed. It remained so for months. Fluid later disappeared; but by then the damage was done. Loss of function was irrevocable, and the lung did not expand enough to obliterate the pleural space completely. Obliteration is still not complete in spite of persistent aspiration of the *ex vacuo* fluid that appeared during reëxpansion. Thoracoplasty is needed; but the patient is reluctant to accept thoracoplasty because she is now clinically well and working.

*Case 2: M. M.* This patient received pneumothorax because of a cavity in the left upper lobe. Collapse was selective except for one adhesion over the involved lobe. This adhesion was severed. Pleural effusion, with fever to 103°F., occurred after pneumonolysis. Immediate excessive collapse of the lower lobe (figure 1A) resulted. But in this case aspirations were started promptly at the rate of every two days. Within two weeks, formation of fluid ceased.

Pneumothorax was then resumed, with small refills to allow further expansion of the lower lobe. The selective and effective pneumothorax seen in figure 1B has been maintained since.

In this case effusion was transient and the same result *might* have been achieved without aspiration. But we are unable to predict in advance how chronic or troublesome a pleural exudate is destined to be. If we wait to make certain, it may be too late to gain our objectives.

*Case 3: D. T.* This patient's problem during an initial clear effusion was much the same as the one just presented, a selective collapse made non selective by the advent of fluid. Again the lower lobe was expanded by frequent aspiration of fluid. Effective pneumothorax was resumed when fluid disappeared (figure 2A).

Later a pure tuberculous empyema occurred and aspirations without air replacement were started. Complete obliteration of the pleural space required 32 aspirations of from 80 down to 10 cc. of fluid, at intervals of from one to two weeks. Finally no more fluid could be obtained.

Figure 2B shows a film made toward the end of the program. The air seen here was admitted after aspiration of fluid at one session only. Its purpose was purely to serve as a contrast medium for roentgenographic and fluoroscopic examination. This procedure helps us to determine accurately whether all fluid present is being aspirated and how much of the total pleuritic density in follow-up films is due to fluid; how much to thickened pleura. Air used for this purpose is removed with the next thoracocentesis.

At the end of the program the X-ray appearance is shown in figure 2C, and no change has occurred since. Total pleuritic density is no greater than that of the thickened pleura demonstrated in the previous film. This provides additional evidence that a residual fluid pocket no longer exists.

The most reliable cure for both serous effusion and tuberculous empyema is exactly the same—complete obliteration of the pleural space. In most cases intensive aspiration is all that is needed to get the pleural space obliterated, unless bronchopleural fistula or major bronchostenosis is present. But thoracoplasty is sometimes needed to expedite obliteration; it is clearly indicated in selected cases for purely mechanical reasons, for example, to prevent excessive shift of the mediastinum and overdistention of the opposite lung. Obviously, thoracoplasty is also the treatment of choice if underlying pulmonary disease requires it.

Thoracoplasty still can't produce pleural symphysis so long as a layer of un-

organized fluid remains interposed between visceral and parietal pleura. Hence, regular aspiration is usually needed, even after thoracoplasty is completed.

*Case 4: E. P.* Figure 3 shows a thoracoplasty performed for caseous-pneumonic disease not adequately controlled by pneumothorax. A tuberculous empyema had developed prior to operation.

The first laminagraphic film at the 14 cm. level (figure 3A) shows an antero-lateral empyema pocket still present twelve months after thoracoplasty. Thirty-three post-operative aspirations had already been done and had ended with dry taps. Eighteen additional aspirations at a new site were required to reduce the pocket to the small size seen in the second sectional film (figure 3B). Aspirations are still being continued.



FIG. 3A. (Left) Case 4. November 2, 1945.

FIG. 3B. (Centre) Case 4. March 12, 1946.

FIG. 4. (Right) Case 6. November 20, 1942.

This is the patient in our 1942 to 1944 series whose pleural exudate is not yet completely eliminated; he is the *only* one who got a needle track infection. This tuberculous sinus in an old needle track has healed completely since the residual empyema pocket was found and was regularly aspirated.

The potential hazards of a persistent pleural dead-space containing unaspirated fluid are well recognized. Yet practice does not always reflect an adequate concern for these hazards. A sizable pocket of fluid may persist for years if one merely waits for spontaneous absorption. Numerous cases could be presented to illustrate the hazards of such persistent pockets of fluid, but 2 will suffice.

*Case 5: J. W.* This patient developed a clear effusion complicating pneumothorax in 1934. A few aspirations were performed, but technical difficulties were encountered

and aspirations were abandoned. Pocketed fluid of moderate amount remained. The pocket did not change for three years. Then an acute exacerbation of the pleural infection occurred and frank bronchopleural fistula developed. Mixed tuberculous and pyogenic empyema and spread of disease to the opposite lung promptly followed. Thoracotomy was immediately performed but the patient grew progressively sicker and died.

*Case 6:* A. T. In 1933 this patient was found to have extensive right sided pulmonary tuberculosis with multiple cavities. A spontaneous hydropneumothorax occurred and pneumothorax was then maintained as a therapeutic measure. It was constantly complicated by pleural fluid but was effective in producing arrest of pulmonary disease. With abandonment of pneumothorax, fluid persisted. The patient left another sanatorium against advice in 1935 with the right pleural space filled with fluid. He managed to get about and to work fairly regularly for seven years. In 1942 we first saw him in a general hospital, acutely febrile and desperately dyspneic. Exacerbation of the pleurisy had occurred with rapid formation of fluid under high pressure. The mediastinum was displaced, and fluid had ruptured through the parietal pleura forming a large, bulging, subcutaneous abscess. This is demonstrated best in figure 4 following incomplete aspiration of pure tuberculous pus and partial air replacement.

Fortunately for the patient, rupture of fluid under pressure occurred through the parietal instead of through the visceral pleura, and the skin over the pleuro-subcutaneous abscess remained intact. It was soon possible to reduce this abscess into the pleural space and to keep it reduced by repeatedly evacuating pus from the pleural space and by thus maintaining a high negative intrapleural pressure. The size of the residual pleural space also became progressively smaller. The space was finally obliterated completely by thoracoplasty and aspiration. The patient has remained well since; but he escaped disaster by a hair's breadth.

In both these last 2 cases pleural fluid *originally* was non-purulent and remained quiescent for several years. Yet the potentially serious consequences of simply leaving fluid alone are apparent.

Late complications of this type cannot occur once the pleural space is completely obliterated by pleural symphysis.

#### SUMMARY

When pneumothorax is complicated by pleural fluid, purulent or non-purulent, simple thoracocentesis is of great value in managing it. Policy in different clinics still varies widely in the frequency and regularity with which thoracocentesis is employed. For maximum effectiveness thoracocentesis must be performed regularly, systematically and intensively, not just occasionally or haphazardly. The objective is to prevent accumulation of more than a very small amount of fluid at any time. In this way one may prevent excessive collapse of uninvolved lower lobes by fluid and expedite obliteration of the pleural space.

Cases are presented to illustrate the value of systematic thoracocentesis. Other cases illustrate the potentially serious hazards of simply leaving fluid alone, even when it appears to be benign.

#### SUMARIO

Si el neumotórax se ve complicado por la preseneia de derrame pleural, ya purulento o no, la toracéntesis simple resulta de mucho valor para atenderlo.

Las distintas clínicas discrepan ampliamente en cuanto a la frecuencia y regularidad con que emplean la punción torácica. Para que dé su rendimiento máximo, hay que utilizarla, no de cuando en cuando o al azar, sino regular, sistemática e intensamente. El objeto es impedir el acúmulo de líquido, salvo en cantidades pequeñísimas. En esta forma puede impedirse el aplastamiento excesivo de los lóbulos inferiores indemnes por el líquido y acelerar la obliteración del espacio pleural.

Preséntanse casos para demostrar el valor de la toracéntesis sistemática. Otros casos patentizan el riesgo potencialmente grave que entraña el líquido si se deja por su cuenta, aunque no parezca nocivo.

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## CHOLESTEROL PLEURAL EFFUSION<sup>1</sup>

LEONARD C. EVANDER

Chronic pleural effusions are common occurrences, but the presence of cholesterol crystals within them must be considered one of the rarest of occurrences. Churton (1882) (1) gave the first description of a case, yet Durham and Diamond (1939) (2) note that only some 20 odd cases had been presented in the literature up to that time. Moreover, they had found their cases in upwards of 26,000 cases admitted with pulmonary disease. Erwin (1941) (3) found no more than 30 cases. Since that time there have been no cases recorded.

Cholesterol effusion, also known as cholesterol pleurisy or cholesterol thorax, is a chronic condition showing little tendency to spontaneous resorption and a marked tendency to recurrence. In practically all cases, there is a history of effusion which occurred years before the discovery of the crystals. The recognition of the complication depends entirely on the recovery of these crystals. The cholesterol content of the effusion will be variable and may diminish with successive aspirations. Moll and Fowweather (8) found that the cholesterol decreased from 260 mg. to 90 mg., within a seven-week period, following repeated aspirations. However, large polyhedral crystals will be found in all fields of the microscope. The fluid, which as a rule has an alkaline reaction, may be clear, turbid or hemorrhagic. It may range in color from light yellow through brown or dark red. There may be few cells in the fluid or several hundred cells or only fragments of cells.

The clinician will not find any typical picture to prepare him for this type of effusion. Due to the long-standing effusion, the pleura is invariably markedly thickened. Though large in amount, the fluid is usually found to be encysted instead of lying free in the pleural cavity. Because of this, though the patient may note some chest pain or slight nonproductive cough or slight dyspnea, there are seldom any pressure symptoms. Fever, rapid pulse or toxemia are usually absent. The condition has been reported mostly in middle-aged adults, nearly all in men. Only one report deals with a child, age 9, who had had an operation for empyema several years previously (Sharpe (4)). In general, cholesterol pleurisy is benign and the patient may carry the fluid for years. One complication has been reported, that of a bronchopleural fistula (Coyon (5)).

The etiology of these cholesterol effusions is not entirely clear. Evidence of pulmonary tuberculosis has been found in less than 50 per cent of cases. Diabetes, syphilis, or a combination of these with tuberculosis have sometimes been considered as causal factors. In some few cases, there has been pulmonary tuberculosis with positive sputum. The greater number of reports have mentioned only a primary effusion, tubercle bacilli being usually absent on concentration or culture and only occasionally identified following the inoculation of guinea pigs with the fluid. One patient died of tuberculous meningitis (Stein

<sup>1</sup>From the Niagara Sanatorium, Lockport, New York.

(6)). The fluid, in this case, contained cholesterol crystals but no tubercle bacilli.

The origin of these crystals is also a matter of speculation. Weems (7) attributes them to lessened resorptive power of the pleura caused by the sclerotic changes present in old age: a generalized thickening of the membranes, an atrophy and obstruction of the lymph and blood vessels. Erwin (3) mentions two factors: first, there is a protracted exudation containing cholesterol derived from the blood stream. Second, there is a progressive thickening of the enclosing membrane with delay in the process of resorption; that is, an isolation from the circulating body fluids and the prevention of any interchange of constituents. It has, however, been found that the blood cholesterol remains at a normal level and that the cholesterol level of the pleural fluid is independent of the blood cholesterol. Moll and Fowweather (8) reviewed the work of Desbordes and his associates (9, 10) and discussed the changing cholesterololytic power of ageing fluids. It has been found, by placing cholesterol in contact with fluids, and then checking by what amount the cholesterol content is increased or diminished, that some fluids increase their cholesterol content; that they have the ability to dissolve the cholesterol. Other fluids show a decreasing cholesterol content; they have a tendency to precipitate out the cholesterol. Following rapid repeated aspirations, the fluid has a strong cholesterololytic tendency, while with ageing, the precipitating action was more noticeable. It may be that some old fluids are supersaturated with cholesterol and precipitate it spontaneously. It is also possible that the fluid has come in contact with a degenerated or caseous focus in which solid cholesterol is present, with precipitation also occurring in this case. This idea would help to explain the chronic tendency of cholesterol effusions. Since all the crystals cannot be removed at aspirations, as the fluid forms and ages, some of the crystals left behind would eventually act as a precipitating agent. Another condition, noted by these workers, was the change in the albumin-globulin ratio accompanying the changing cholesterololytic action. The total protein remained constant, but with an ageing fluid there was a decrease of the albumin and an increase of the globulin. Thus, with the ratio greater than one, the fluid had a cholesterololytic tendency, and a precipitating action with a ratio under one. The conclusion drawn was that this ratio is the determining factor in the formation of the cholesterol crystals in the fluid. Durham and Diamond (2) suggest that if these fluids are tuberculous in nature, perhaps the crystalline cholesterol is associated with the destruction of the tubercle bacillus and an alteration of its lipid constituents.

Considering the chronic character of cholesterol effusions, it would appear advisable to aspirate the fluid only if symptoms are present. Repeated aspirations would probably not eliminate the fluid or the pleural space, but might lead to secondary infection.

#### CASE REPORTS

*I. S. S.*—A married white woman admitted to Niagara Sanatorium on October 26, 1918; age 23. The patient's past history revealed that she had been in good health until



August, 1934. At this time, and again in May, 1937, she required hospitalization for the removal of considerable amounts of pleural fluid. Sputum and fluid examinations were negative for tubercle bacilli, and the X-ray examination showed no evidence of parenchymal infiltration. In October, 1938, because fluid was again noted on an X-ray film and hemoptysis was present, sanatorium admission was advised. The admission roentgenogram showed the right thorax to be completely obliterated by a dense shadow, from clavicle to base. The heart and mediastinum were markedly displaced to the left, with left heart border nearly coincident with the left chest wall. From the right chest 700 cc. of straw-colored, oily-appearing material containing supernatant flecks of a crystalline substance were aspirated. This fluid was reported by the laboratory to contain a considerable number of cholesterol crystals and a few epithelial cells showing fatty degeneration. There were no tubercle bacilli or other organisms. Specific gravity was 1.015; reaction was neutral. Differential count was: polymorphonuclear leucocytes, 16, lymphocytes, 84 per cent. The patient's Wassermann reaction was negative. Sedimentation rate was 22 mm. in the first hour. Blood and urinary findings were within normal limits. Fluid, ranging in amount from 500 to 1,250 cc., was removed first at weekly intervals and later at irregular intervals. A routine X-ray film in July, 1939 showed fluid on the right to the level of the eleventh posterior rib. The right lung showed only some pleural thickening. The last aspiration was done in July, 1940. The fluid was still straw-colored but slightly turbid and still contained cholesterol crystals. The patient was discharged in September, 1940 and followed in the clinic. At her last examination in April, 1945, Bucky, deep penetration and oblique films revealed only thickened pleura and a dense shadow obscuring the right base. The patient had been working in an airplane factory for the past two and a half years. She was feeling very well and had no chest pain, cough or expectoration.

*Comment:* This case differs from the other reports in that we are dealing with a woman, in the younger age group. Some features of cholesterol effusion are shown by the four-year history of effusion prior to the discovery of the cholesterol crystals, the markedly thickened pleura, the recurrence of the fluid and the benign course. The only indication of tuberculosis was a primary complex. The fluid never contained tubercle bacilli on concentration or culture.

2: C. S.—A single white woman admitted to Niagara Sanatorium on June 24, 1933; age 20. Her past history revealed fatigue, poor appetite and chest pains of three years duration. Admission X-ray film revealed mottled infiltration from the left apex to third anterior rib, as well as some calcification in the right hilum. Though the sputum was negative for tubercle bacilli, left pneumothorax was induced in July because of increasing disease. In August, 1936, a slight amount of fluid was present in the left costophrenic angle and the base of the lung was adherent to the chest wall. By March, 1937, the lower half of the lung had become adherent. The pneumothorax was discontinued at this time. Subsequent X-rays films, before discharge in January, 1939, showed a homogenous shadow over the left lateral portion of the chest. Because of infiltration in the right subclavicular area, readmission was necessary in May, 1939. Two years later, the density in the left chest was seen to extend from the clavicle to the ninth posterior rib. A small amount of clear, straw colored fluid was removed at this time. The fluid, as well as the sputum, was negative for tubercle bacilli. At another aspiration in March, 1942, the fluid was found to be turbid, greenish-yellow, specific gravity 1.033, and still negative for organisms. On March 9, 1946, the patient developed pain in left chest and temperature

up to 104°F. The density on the left had increased. The chest was, therefore, aspirated with the removal of 400 cc. of moderately thick, oily, brownish fluid. This material was filled with cholesterol crystals and questionable leucocytes, but no organisms. The types of cells still could not be determined, because of the numerous cholesterol crystals. Following the aspirations the patient's temperature came down to 99.4°F. On March 20, the fluid was still oily, turbid, yellow-brown. The cholesterol determinations were: in pleural fluid 101 mg. and in blood 192 mg. per 100 cc. The sedimentation rate was 48 mm. in the first hour. Hemoglobin, 12 g.; red cells 5,000,000; white cells 7,500; segmented 48; stab 20; lymphocytes 24; monocytes 6; eosinophils 2. On April 11, 75 cc. of cloudy, orange-amber fluid containing many crystals were removed. The temperature was now between normal and 99.2°F. X-ray examination revealed only marginal haziness on the left side and cavitation on the right. The sputum was positive for tubercle bacilli, but the fluid was still negative for tubercle bacilli, fungi or other organisms. On smear, the fluid was loaded with cholesterol crystals and debris; no cell count could be done but a few leucocytes were seen. The fluid had a specific gravity of 1.022; pH 7.7; cholesterol 103 mg.; total protein 4.5 per cent; albumin 2.9 per cent; globulin 1.6 per cent. The blood showed cholesterol 179 mg.; total protein 7.3 per cent; albumin 4.3 per cent; globulin 3.0 per cent; sedimentation rate 34 mm. hemoglobin 12.4 g.; red cells 4,700,000; white cells 10,250; segmented 45; stab 22; lymphocytes 31; monocytes 1; basophiles 1. An X-ray film, three months later, showed slightly increased haziness. No further aspirations have been required.

*Comment:* This is the case of another woman, age 33, instead of the usually reported older-aged males. This patient had chest pain and elevated temperature. Aspirations appeared necessary and were done until the patient was asymptomatic. Again, some of the features of cholesterol effusions were noted: fluid, following pneumothorax therapy, nine and one-half years prior to discovery of cholesterol crystals; the fluid was pocketed and the pleura was thickened; so many crystals were present that a cell count could not be done; the color varied; the fluid was sterile. The 1.8 albumin-globulin ratio of the fluid would indicate that the fluid was in the cholesterolytic stage. This is probably due to the fact that the ratio was determined after repeated aspirations, after new fluid had an opportunity to form. The patient had active pulmonary tuberculosis requiring pneumothorax therapy.

#### SUMMARY

Two women with chronic recurring pleural effusions containing cholesterol crystals are presented. The findings are reviewed regarding the etiology and pathogenesis of this rare occurrence in previously reported patients.

#### SUMARIO

Preséntase a dos enfermas con derrames pleurales recurrentes crónicos que contenían cristales de colessterina. Repásanse los hallazgos relativos a la etiología y patogenia de este raro fenómeno en los enfermos previamente descritos.

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# EXTRAPLEURAL PNEUMOTHORAX IN SILICO-TUBERCULOSIS<sup>1,2</sup>

H. M. MAHER AND A. HURST

Collapse therapy of silico-tuberculosis presents a difficult problem. The marked fibrosis in the silicotic areas forms a resistant barrier to collapse of the lung. The loss of respiratory function due to destruction of lung parenchyma by the combination of two pathological processes is another obstacle to collapse therapy. Auerbach<sup>1</sup> in a post-mortem study of 51 cases of silico-tuberculosis reported 8 attempts at artificial pneumothorax, all of which were ineffective. Four patients had undergone thoracoplasty operations, 2 of which died from shock and paradoxical respiration immediately following the first stage. The other 2 died following three stages and revision; patent cavities were found in the lungs in all cases. Based upon these findings he stated "we have found collapse therapy of little value in cases of silico-tuberculosis."

The ability of the silicotic lung to retract following collapse therapy cannot be adequately predicted from physical and X-ray findings. In addition the question of activity of the silicotic process itself is an important consideration and requires long-term observation. In view of these facts and of the poor results of surgical collapse the predominant attitude in the treatment of silico-tuberculosis has been a rather conservative one. A case of silico-tuberculosis is reported in which surgical collapse was done using extrapleural pneumothorax.

<sup>1</sup> From the National Jewish Hospital at Denver and the University of Colorado School of Medicine, Denver, Colorado.

<sup>2</sup> In the United States the term *silico-tuberculosis* is quite generally used to designate any combination of tuberculous and silicotic lesions. However, this usage does not differentiate between two very definite categories of disease and is at variance with the nomenclature of the Miners' Phthisis Bureau of Johannesburg, South Africa, where the term was originally coined.

In South Africa *silico-tuberculosis* means any of a number of combinations of silicosis and tuberculosis in which the infection is manifested by typical clinical symptoms and pathological-anatomical findings. The silicotic nodulation remains discrete and uniformly distributed. The tuberculous lesions usually develop in a normal manner upon a background of nodular fibrosis, although sometimes there may be acute perinodular tuberculous reaction. The ordinary clinical course is that of tuberculosis in an otherwise normal subject. Such cases are comparatively rare.

Much more common is the specific disease *tuberculo-silicosis*. In this instance the silicotic lesions are themselves modified by chronic tuberculous infection. The characteristic lesion is a massive fibroid consolidation with or without apparent generalized nodulation in other parts of the lungs. Contraction and compensatory emphysema may interfere with X-ray visualization of the discrete nodules outside the conglomeration. The tuberculous infection responsible for the massive fibrosis may be healed and free of specific organisms, or it may be latent and ultimately manifest itself with classical symptoms of tuberculosis. This special form of disease runs an unusually chronic course; symptoms of infection and tubercle bacilli in the sputum are delayed until a year or so before death. Since neither the pathological nor the clinical aspects of tuberculo-silicosis are produced by either tuberculosis or silicosis alone, there is every reason to conform to South African usage to restrict the term *tuberculo-silicosis* to this unusually chronic combination of infection and silicotic fibrosis. [L. U. GARDNER]

## CASE REPORT

C. P., a 39 year old white male, superintendent of a rock-grinding mill with exposure to silica dust for twelve years. X-ray film on admission to the institution, on August 17, 1942, showed a symmetrical dissemination of nodular infiltrations throughout both lungs, and a 3.5 cm. cavity in the left upper lobe. Sputum was positive for acid-fast bacilli on direct smear. In view of the occupational history and the appearance of the X-ray film, a diagnosis of silico-tuberculosis was made. Patient was treated conservatively and serial films showed progression of the nodular infiltration from May, 1942 until December, 1943, suggestive of progressive silicotic involvement. Thereafter the roentgenogram showed no further progression of the silicotic process with the cavity



FIG. 1

FIG. 2

FIG. 1. Film of October 12, 1945, before extrapleural pneumothorax.

FIG. 2. Film of April 25, 1946, after institution of extrapleural pneumothorax was begun.

essentially unchanged in size. Pneumothorax was attempted unsuccessfully, phrenic nerve crush was performed and pneumoperitoneum instituted without therapeutic effect. He remained on modified bed-rest and was given a course of chemotherapy (diasone) in 1944, with no change in his condition. The cavity persisted and the sputum remained frankly positive. On November 6, 1945 an extrapleural pneumothorax on the left was performed by Dr. S. Reckler. Following the operation the usual routine was followed with careful fluoroscopic and X-ray follow-up, repeated aspiration of the extrapleural space and air refills maintaining extrapleural pressures up to 50 cm. of water. X-ray films showed a satisfactory collapse and the cavity which was still seen following the operation, although greatly reduced in size, closed under increased compression. The sputum was converted ten weeks after the operation and has since remained negative on culture. In view of the good result it was felt that no additional surgical collapse was needed and

extrapleural oleothorax was done following the usual graded procedure. The patient is going through the rehabilitation phase at present, on full exercise and will be discharged in the near future.

#### COMMENT

Cases of conglomerate massive silico-tuberculosis with necrosis and secondary infection are undoubtedly difficult if not impossible to treat actively. The nodular disseminated form of silicosis with tuberculous cavitation in one or both upper lung fields should lend itself to collapse therapy more readily. Since pneumothorax is frequently impossible, the only other reversible procedure is that of extrapleural pneumothorax which may be used to test the ability of the cavity to close as well as a direct measure of the patient's respiratory reserve. As a preliminary measure before thoracoplasty, it should be of real value. In the case reported, pneumothorax was unsuccessful, and phrenic and pneumoperitoneum of no benefit. The X-rays showed no real change for three years and although surgical collapse had been considered on many occasions, it was doubted that the cavity could be closed by such measures within a rigid lung. Extrapleural pneumothorax was recommended as a trial procedure to test the ability of the lung to retract and as a measure of respiratory reserve.

#### CONCLUSION

Extrapleural pneumothorax was used in a patient with silico-tuberculosis with prompt closure of the cavity. It is a useful procedure because of its reversible character.

#### CONCLUSIONES

En un enfermo con tuberculosilicosis empleóse el neumotórax extrapleural, obteniéndose la rápida obliteración de la caverna. El procedimiento resulta útil debido a su naturaleza reversible.

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## TUBERCULOSIS—A LABOR PROBLEM

LEO PRICE<sup>1</sup>

Tuberculosis to the worker means loss of a job, prolonged residence in a charity institution, worry about impoverished dependents and trouble in finding another job if he ever gets well again.

Viewing tuberculosis in this manner, Labor classifies the disease not from the point of view of pathology but from the basis of the different economic problems to be solved:

- 1st: The married worker with a wife and two or more children dependent upon him for their entire support.
- 2nd: The married tuberculous woman worker whose earnings supplement her husband's wages, or who is the sole support of a few fatherless children.
- 3rd: The custodial tuberculous worker, a 65 year old grandfather who must still work, although he has a cavity and will probably always have a positive sputum. He furnishes an added problem when he lives in the home of a married daughter who has children.
- 4th: The unmarried tuberculous young worker.

None of these different groups, as a rule, have any substantial amount of money to take care of prolonged illness. When wages stop abruptly because of disability, they face the prospect of seeking charity.

Organized Labor has had little means to tackle this problem properly. In the past, Labor has not been apathetic about looking for a solution, but economic conditions have prevented Labor from setting aside sufficient funds for tuberculosis control. Industry has done little, except for a very few of the larger industries which have made provision for tuberculous workers, and most industrial insurance policies exclude payment to tuberculous workers.

Educational campaigns to find tuberculosis early, with emphasis on the dire consequences of neglect, have only added fear without putting stress on solving the economic problems and alleviating the mental distress of its victims.

If a program were drawn up so that a worker who discovers he suffers from tuberculosis also knows definitely the extent of medical and economic aid of which he is assured, coöperation with case-finding procedures might be more successful. Ideally this assurance should comprise weekly cash indemnities for dependents, sanatorium or hospital care and opportunity for family reunions at intervals during institutional residence. But most important of all is the promise of a job when the patient can again return to work and the assurance that medical supervision will be available to keep him well.

To-day medical art and science do much in caring for the tuberculous patient while he is actually ill and in a hospital or sanatorium. Modern treatment enables many a patient to return home in good physical condition. However, not as much has been done to keep him in that condition while he continues to

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earn his living and resumes his domestic responsibilities. Most frequently he returns to a family which suffers from financial insecurity through the loss of income caused by his long illness; there are little or no provisions for a gradual preparation of the handicapped tuberculous "cured" patient in sheltered workshops until he is on equal terms with his fellow workers. He is expected to compete in the labor market with men who are physically able to sustain the heavy eight-or-more hour working day. Competition, piece-work payments, together with anxiety and insecurity, may lead to reactivation and continue to present a most vexing problem to the program of prevention and control of tuberculosis.

The International Ladies Garment Workers' Union has long realized that tuberculous workers need to have definite economic as well as medical help to fight this disease. It has also made certain from the very beginning of its program that the worker would be able to resume work in the industry after the disease was arrested.

The Cloak Pressers' Union established the first tuberculosis insurance fund in 1913. The phenomenon of a labor group attempting to fight tuberculosis resulted from the dramatic demonstration of the need for this fight. A survey by the U. S. Public Health Service of 3,000 pressers in New York City demonstrated the high incidence of tuberculosis in the industry. It found that 3.11 per cent of the male workers and 0.9 per cent of the female workers were afflicted with the disease. The publication of the results of this study in the U. S. Public Health Service Bulletin No. 71 also revealed the generally deplorable state of health of most of the surveyed group and their crying need for medical care.

In addition, the Union realized that if the prevailing unsanitary working conditions which aggravated and spread the disease were unchanged, tuberculosis would remain a serious threat to the health of the workers. There followed the first program sponsored by both the Union and management to clean up the unhealthy sweatshop conditions prevailing in the garment trades. The Joint Board of Sanitary Control (the parent of the Union Health Center) had been founded in 1910 to supervise this unique industrial health program.

In spite of the fact that the Union was confronted with its own economic problems, this labor organization made a modest start at developing a tuberculosis and health program. During the following years other crafts of the Ladies Garment Workers' Union followed the example of the pressers by developing tuberculosis insurance and eventually sick benefit insurance programs. Although 22 of the 30 New York City local unions have now adopted different programs of their own choosing, basically the plans are very similar, varying only in detail.

At the very beginning the premium charged to the workers in the form of a tuberculosis tax was \$1 or \$2 per member a year. Where tuberculosis and sickness insurance benefits were merged, the premium rate, as a rule, was \$4.20 a year. The original benefits covered were sanatorium care for the tuberculous or cash payments of \$150 to \$350; cash indemnities during other disabling illnesses of \$7 a week for ten weeks; two free examinations a year at the Union Health Center, which was founded in 1916 to furnish ambulatory medical service.



Physical examinations were offered as a preventive measure to appraise the health of the worker and discover diseases at an early stage before they became severe and incapacitating. All new members who joined local unions with health plans had to undergo a physical examination before participating in the benefits provided by the health funds.

All locals contributed substantial sums annually to three different sanatoria so that tuberculous workers would be assured of admission.

In this program was also included the supervision of tuberculous workers after the disease was arrested, when they were permitted to return to work subject to periodic medical examination.

Twenty years ago at the 21st annual meeting of the National Tuberculosis Association in 1925, Dr. George M. Price, the founder and then Director of the Union Health Center, gave a résumé of the accomplishments of the Union's fight against tuberculosis in which he stated:

"During the last twelve years, more than 36,000 candidates for membership in the union were examined in New York City alone and of these 40 persons with active pulmonary tuberculosis and positive sputum were rejected. A great many of those who were suffering from tuberculosis in a milder, inactive form, have had their admission to the union postponed until their disease was stabilized.

"In addition to the examination of candidates, there were about 35,000 examinations made of union members during the last ten years. Five hundred members have been found suffering from active pulmonary tuberculosis and have been taken out of the shops, tuberculosis benefit paid to them, either in cash or in the form of payment of their board and lodging at a sanatorium or boarding house in Liberty, N. Y., or some other place, by the union, for a period often up to twenty-five weeks. During the time that the members were in sanatoria or boarding houses, they were under medical supervision and were not permitted to work before their disease was arrested.

"One local, that of the Pressers, with 5,000 members, took care of 129 cases of active pulmonary tuberculosis within the last ten years."

This description of the early fight by the Ladies Garment Workers' Union against tuberculosis may be referred to as the first period. While the case-finding methods were good for the time, they were not comparable with present day procedures. The general physical examination of new members who joined those unions which had a benefit program may have been effective in the early years when older workers applied for membership. However, X-ray and laboratory diagnostic procedures were not utilized because such routines were too costly. The periodic health examinations of union members formed a source of case-finding among those who had definite complaints or took advantage of the medical service offered.

The second period began in 1934, following the National Recovery Act when there was great growth in the economic strength of unions. The physical examination of new members continued but only rare cases of tuberculosis could be discovered in the younger age workers who now entered the industry. There was, however, a new case-finding method developed when some of the financially stronger union groups were able to permit careful physical review, including the

use of X-ray and laboratory procedures, of all claimants for sickness indemnities who had upper respiratory conditions. With these additional methods of case-finding, many more cases of tuberculosis were uncovered.

In the ten years from 1935 to 1944, 481 cases of active pulmonary tuberculosis were discovered, of which 287 cases were awarded tuberculosis benefits by the Union Health Center on behalf of the local unions. The distribution of benefits may be seen in table 1.

Other cases of tuberculosis probably existed among I.L.G.W.U. members who were in locals which at that time had no provision for tuberculosis benefits; and unfortunately the data are not entirely complete for the cases recorded. Nevertheless the data accumulated during this period reveals much of interest.

TABLE 1  
*Yearly study of cases of active pulmonary tuberculosis*  
*National Tuberculosis Association Classification*

YEAR OF DIAGNOSIS OF DISEASE	TOTAL CASES FOUND	CASES AWARDED BENEFIT	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED
Total.....	451	287	77	132	78
1936	49	36	9	21	6
1937	58	38	5	17	16
1938	53	30	6	19	5
1939	102	48	11	26	11
1940	54	40	21	11	8
1941	51	41	10	15	16
1942	33	28	11	11	6
1943	28	11	3	5	3
1944	23	15	1	7	7

The number of cases of active tuberculosis discovered was dependent upon:

- 1: The number of health programs in operation.
- 2: The methods of case-finding applied.
- 3: The working activity and economic conditions of the industry.
- 4: The opportunity to X-ray Sick Benefit Claimants.
- 5: The opportunity to improve the quality of medical examinations.

The third period began in 1939 when Dr. Herbert R. Edwards of the Bureau of Tuberculosis of the New York City Department of Health inaugurated plans for mass chest X-ray examinations of industrial groups. An X-ray survey of 23,974 members of the International Ladies Garment Workers' Union was made by the New York City Department of Health and the United States Works Progress Administration. A synopsis of the number of X-ray examinations done and the findings reported may be observed in table 2.

A word may be given concerning the composition of the different local groups examined. The dressmakers, which include Locals 10, 22, 60 and 89, are mostly older workers. Locals 22 and 89 are composed primarily of women members,

with about 85 per cent of the former and 95 per cent of the latter being women. Locals 10 and 60 are primarily men, very few women being present in either group.

The age distribution in these four groups of dressmakers during 1939 was: 20 per cent below the age of 30; 26 per cent in the third decade of life; about 35 per cent over 40; and 17 per cent 50 years or over. More than 80 per cent were foreign born.

Among negligée workers, Local 62, a younger age distribution prevailed, with 60 per cent under 30 years of age and 24 per cent in the third decade of life.

TABLE 2  
*Analysis of 1939 tuberculosis survey*

LOCALS PARTICIPATING	NUMBER OF MEMBERS EXAMINED	PER CENT MEMBER-SHIP EXAMINED	CLINICALLY SIGNIFICANT CASES STUDIED		ACTIVE TUBERCULOSIS		INACTIVE TUBERCULOSIS CASES	
			Number	Per cent	Number	Per cent	Number	Per cent
Total.....	23,974		106*	.44	57	.24	430	1.79
62	6,437	64.6	29	.45	16	.25	88	1.37
91	5,660	64.0	20	.35	11	.19	65	1.14
22	5,440	20.6	29	.53	16	.29	140	2.57
155	2,546	74.0	12	.48	8	.31	40	1.57
89	1,698	5.0	4	.24	1	.06	25	1.47
10	521	7.2					11	2.11
117	512	5.5	3	.59	1	.20	24	4.69
60	399	11.4	2	.50	1	.25	13	3.26
32	262	8.7	1	.38	1	.38	5	1.91
40	162	9.0	2	1.23	1	.62	4	2.47
132	98	5.6	3	3.06	1	1.02	1	1.02
Others†	249						6	2.41
No Local			1				8	

\* 49 of this group were considered as inactive cases by the Union Health Center and have been working under medical supervision.

† Includes Locals 9, 23, 35, 64, 66 and 142.

About 40 per cent were foreign born, with very few native born of native parents. Ninety-nine per cent of the membership were women.

The major age distribution of the Knitgoods Workers, Local 155, is in the younger brackets with 40 per cent under 30 years old, 28 per cent in the third decade of life and 14 per cent in the fourth decade. Sixty-one per cent were women and 39 per cent men.

Local 91, the Childrens' Dress Workers, consist of a 93 per cent women membership. Those under 30 numbered 39 per cent; 16 per cent were in the third decade and 22 per cent in the fourth decade of life. The largest group (60 per cent) were native born of foreign born or mixed parentage; 40 per cent were foreign born.

The 1939 survey reported 106 members as having clinically significant findings deserving further medical supervision to determine the possible need of sanatorium care. Table 2, column 3, records the percentage of the membership that were X-rayed. The Health Center made complete medical investigation and found that 57 of these 106 members had active pulmonary tuberculosis. They were not permitted to continue to work in the industry, but were provided with tuberculosis benefits, hospital or sanatorium care. After the disease was stabilized, upon application they were given an opportunity to return to work in the industry under medical supervision.

All other cases suspicious of pulmonary tuberculosis were further studied and classified as inactive.

Table 3 reflects the interest displayed by the different union groups in investigating the presence of tuberculosis since the 1939 survey.

The great advance in case-finding through the survey method stems from the

TABLE 3  
*Chest X-ray studies of garment workers in New York City*

LOCAL	DATE SURVEY	WORKERS X-RAYED		TUBERCULOSIS CLASSIFICATION			
				Inactive		Active	
		Status	Number	Number	Per cent	Number	Per cent
155	June, 1945	Members	4,294	76	1.77	1	0.02
155	Oct., 1945	New Members	408	5	1.23	1	0.25
155	Feb., 1946	New members	600	4	0.67	1	0.16
40	Feb., 1946	Members	2,069	62	3.00	1	0.05
*40	Apr., 1946	New members	560				
142	May, 1946	New members	516	14	2.71	0	

\* Final figures not completed.

opportunity to screen large groups of workers to discover cases with minimal lesions, hitherto rarely uncovered by former case-finding methods. Recognition of the presence of the disease before the patient presents clinical symptoms insures an earlier and more certain cure, a minimum loss of time from work and a protection to others. X-ray suveys, in conjunction with a program of careful physical examinations and the supervision of admission, may lead to the elimination of tuberculosis in the industrial groups thus controlled, provided the full coöperation of the workers and financial provisions are made freely available.

The present era may be said to have begun in 1942 when the union contracts first contained a clause whereby the manufacturers agreed to pay a tax of 1.5 per cent of the payroll for medical service to employees. This innovation provides funds for a more thorough and complete tuberculosis program.

However, in 1943 and 1944, during the period of the greatest war-production activity in the industry, when earnings reached their highest point in history,

workers were unwilling to miss the high earnings and continuous work. Therefore they refused to take time off to guard their health and the number of tuberculosis cases discovered dropped sharply to reach the lowest level in the ten-year period, a level that is merely apparent but not real.

In a selected group of 287 cases studied from 1935 to 1944, 35 per cent of the tuberculosis cases were men and 65 per cent were women, as shown in table 4. During the period covered, probably 80 per cent of the workers in the garment industry were women, principally under 30 years of age, many of whom do not remain in the industry for a long continuous period. The men, however, are mostly over 40 years of age and remain in the industry throughout their working life.

TABLE 4  
*Age and sex of 287 tuberculosis patients*

	TOTAL	UNDER 20	20-29	30-39	40-49	50-59	60 PLUS	UNKNOWN
Total.....	287	11	134	40	48	40	10	4
Males.....	101		14	10	28	38	10	1
Females.....	186	11	120	30	20	2		3

TABLE 5  
*Marital status of 287 tuberculosis patients*

	TOTAL	SINGLE	MARRIED	WIDOWED, DIVORCED OR SEPARATED	UNKNOWN
Total.....	287	102	162	13	10
Males.....	101	12	79	6	4
Females.....	186	90	83	7	6

Workers under 30 years of age, both male and female, comprise 51 per cent of the cases of active pulmonary tuberculosis discovered, with an additional 14 per cent of the cases discovered being in the third decade of life. This means that 65 per cent of the workers found to have tuberculosis were under 40 years of age.

Among the men afflicted with tuberculosis, 75 per cent were more than 40 years old. At that age men usually have families to support and children to educate, while they have lost the strength of youth to overcome the hardship of disease and worry.

Among the women, 70 per cent were under 30 years of age and another 16 per cent were in the 30 to 40 age group—86 per cent of the women with tuberculosis were less than 40 years old.

The marital status of the group studied (table 5) shows 35 per cent of the tuberculosis patients were single and 65 per cent were married. Among the men only 13 per cent were unmarried, although 50 per cent of the women were un-

married. The prevalence of active tuberculosis among the younger women, many of whom are married and in the child-bearing age, presents a special problem of workers' tuberculosis control. This is especially true among the women who work in the industry and also carry the burden of caring for the home. More vigorous and thorough tuberculosis control is needed, not only for the workers alone but also their family contacts.

Table 6 lists the National Tuberculosis Association's classification by the sex of the patients.

Only about one-quarter of all cases of tuberculosis were classified as minimal, that is, 19 per cent of the men and 31 per cent of the women workers. Present-day methods of diagnosis can discover minimal pulmonary tuberculosis; findings of this sort dramatically point-up the need for a vigorous control campaign to reverse the proportion found.

In spite of thirty years of tuberculosis control in the garment industry, it seems the problem of discovery of minimal disease is still unsolved. However, the experience demonstrates that successful attack upon the problem depends upon the

TABLE 6  
*Tuberculosis classification by sex*

	TOTAL	CLASSIFICATION OF PULMONARY TUBERCULOSIS		
		Minimal	Moderately advanced	Far advanced
Total.....	287	77	132	78
Males.....	101	19	48	34
Females.....	186	58	84	44

adoption of a definite policy and the allocation of adequate funds. Labor cannot afford to eliminate workers who show evidence of arrested tuberculosis. However, Labor should register all such cases and keep them under medical supervision so that they do not break down and become a menace to themselves, their families, their labor organization and the community. If such arrested cases do break down, the workers should receive the essential care as soon as possible, so that they can be more easily rehabilitated.

Moderately advanced tuberculosis was found in approximately half the cases classified, and occurred in practically the same proportion in the men as in the women workers. Far advanced tuberculosis occurred in 34 per cent of the men and 24 per cent of the women. In both men and women, moderately advanced and far advanced tuberculosis predominated, with about 80 per cent of the men in these classifications and approximately 70 per cent of the women.

The age groupings of the men with tuberculosis show that fewer men in each age group were classified as minimal tuberculosis. In the women the smallest percentage in each age group were far advanced cases.

Of all cases of tuberculosis, men over 40 comprised 79 per cent of the minimal

cases, 71 per cent of the moderately advanced cases and 79 per cent of the far advanced cases.

Of the 58 minimal cases of tuberculosis in women, 88 per cent were in women under 40; of the 84 cases of moderately advanced tuberculosis in women, 89 per cent were in women under 30; and of the 44 cases of far advanced tuberculosis in women, 82 per cent were in women under 40.

The record of the status and disposition of cases at the time of diagnosis and the awarding of tuberculosis benefits is of interest because it reflects the type of care selected or made available to workers under the health programs of the past.

In table 7 the term hospital applies to institutions that admit patients for any disease. It also includes the tuberculosis hospitals of the Metropolitan area, such as Seaview, Seton, Triboro and so forth. Sanatoria are considered institutions devoted exclusively to tuberculosis.

Of the 287 patients with active pulmonary tuberculosis, 45 per cent entered sanatoria, 8 per cent entered hospitals and 47 per cent chose to be supervised

TABLE 7

*Patients admitted to tuberculosis hospitals or sanatoria, by tuberculosis classification*

CLASSIFICATION	TOTAL	TOTAL CASES IN SANATORIA	CASES IN AFFILIATED SANATORIA	CITY AND STATE SANATORIA	OTHER SANATORIA	TOTAL CASES IN HOSPITALS	CITY HOSPITALS	OTHER HOSPITALS	NOT HOSPITALIZED
Total.....	287	129	59	44	26	23	15	8	135
Minimal.....	77	34	9	17	8	1	1		42
Moderately advanced.....	132	60	34	15	11	9	4	5	63
Far advanced.....	78	35	16	12	7	13	10	3	30

outside the hospital or sanatorium—in most cases by private physicians and clinics.

Of the 129 persons (45 per cent of all cases) who entered sanatoria, 59, or 21 per cent, were admitted to one of the three affiliated sanatoria which receive support from the unions; 15 per cent entered state or municipal sanatoria and 9 per cent other sanatoria. About one-quarter of these patients had minimal tuberculosis, one-half had moderately advanced tuberculosis and one-quarter far advanced tuberculosis.

Of the 23 persons (or 8 per cent) hospitalized, about 63 per cent entered city hospitals and 37 per cent were admitted to voluntary hospitals. In the hospitals the proportion of patients with minimal, moderately advanced and far advanced tuberculosis occurred in the ratio of 4 per cent, 39 per cent and 57 per cent, while in those who were neither in the hospital nor a sanatorium, the proportion was 31, 47 and 22, respectively.

#### WORKING CARD CASES

When an ILGWU member with tuberculosis has recovered to the extent that his condition is classified as arrested, he may return to work in the industry under a "working card"

privilege. This card is a work authorization issued by the Health Center for a specified period, at the end of which time the patient must be reexamined to make certain there had been no reactivation. As years went on a stigma became attached to these working card cases, because they were identified as tuberculous in the minds of uninformed co-workers. Therefore it seemed a wise policy to modify the stringency of the check-ups after supervision for three years, when complete laboratory and X-ray investigation proved the condition to be completely arrested and stabilized. The former tuberculous worker could then be admitted as an active member of the union with full privileges.

A total of 161 patients with chronic or arrested tuberculosis have worked under the supervision of the Union Health Center during the past few years. This group included workers who had received tuberculosis benefits and had been rehabilitated and returned to the industry. It also included patients of the clinic in whom findings suspicious of active tuberculosis were discovered and newly admitted members to the industry who required supervision to prevent a possible breakdown or to ascertain stability of a lesion. Fifty-one per cent of those supervised were men and 49 per cent were women. Twenty-seven per cent of those supervised are still reporting for periodic check-ups; 40 per cent have been discharged from supervision of the Center; 33 per cent have left the industry of their own accord. Of the 161 cases under supervision, 65, or 40 per cent, were supervised longer than three years.

The number of "working cards" issued to individual members has varied. It depends upon how long the patient remains in the industry, how long he has spent in a sanatorium before discharge, the frequency of reexamination as determined by the supervising physician and other factors. One member received twenty working cards before he was discharged from medical supervision.

Surveys conducted by local groups have a marked effect on the number of tuberculosis cases supervised yearly. Immediately after a survey the supervision load sharply increases.

#### TIME LOST BY WORKING CARD MEMBERS

A study was made of 73 working card cases to ascertain the amount of time lost from work by the group. It was found that 33 per cent lost only six months or less from work before they were well enough to return; 18 per cent lost from six months to one year; 14 per cent lost from one to one and one-half years; 6 per cent lost from one and one-half to two years.

Further study is indicated to determine how much time in rehabilitation and family adjustment is needed before workers can return to the industry and how much additional working time is lost through these procedures.

#### DEATHS FROM TUBERCULOSIS

The deaths from tuberculosis which occurred among garment workers from 1938 to 1945 have been analyzed. Most of the people in this group were known to have tuberculosis, but some died from tuberculosis without having previously been registered as tuberculosis cases.

Of this group, 46 per cent were women and 54 per cent were men; 75 per cent



of the women who died from tuberculosis were under 40 years of age; 86 per cent of the men were over 40 years old. This coincides with the incidence of tuberculosis found among garment workers in the different age groups.

TABLE 8  
*Deaths from tuberculosis by age and sex*  
1933-1915

SEX	TOTAL	20-29	30-39	40-49	50-59	60 AND OVER	UNKNOWN
Total.....	67	14	13	5	26	7	2
Male.....	36	2	3	3	21	7	
Female.....	31	12	10	2	5		2

#### BETTER CONTROL

Mass X-ray surveys to discover and treat early tuberculosis may have a definite influence upon the age of death of the tuberculous patient. The acceptance of the importance of X-ray surveys by Labor may result in the acceptance by every local union of a thorough and complete program for the control and eventual eradication of tuberculosis from the industry.

The general physical examination of candidates for membership before they are eligible for benefits from the health fund is gradually being discontinued in most local unions which have acquired payroll tax levies for health. In place of this examination, some groups have adopted regulations requiring a chest X-ray examination, urinalysis, a hemoglobin and Wassermann test as preliminary to union membership. The entire membership of such groups is now entitled to numerous health benefits, usually after collection of an employer tax on their income for a six-month period of employment.

With additional funds now available, the Center has been able to use still another vigilant method of case-finding. Whenever a tuberculous worker with positive sputum is discovered at the Center, either as an applicant for admission to the union, as a patient or as a claimant for sickness insurance, the Center has had little difficulty in persuading the union to survey all other workers in that particular shop. A most unusual recent experience in a shop in the beltmakers' union (Local 40, see table 3) stimulated that union to make a chest X-ray survey of its entire membership.

A young Italian girl worker in a leather goods manufacturing plant died from unsuspected tuberculosis. In an effort to find the source case a thorough survey was conducted of the 42 workers in the shop in which she was employed. Four workers in this small group were discovered to have active pulmonary tuberculosis, one with a minimal lesion of questionable activity, one far advanced, bilateral with cavities on both sides and positive sputum, and 2 moderately advanced. Of the latter, one had a positive sputum although on X-ray examination the lesion appeared inactive.

There were also found 3 persons with old fibro-calcific apical lesions, probably healed and inactive. One of the older workers who had a fibro-calcific apical lesion was first considered a suspicious case requiring careful investigation because of the extensive nature of the lesion. Four consecutive sputa examinations were negative, but a gastric lavage yielded tubercle bacilli on culture. Since one gastric lavage was found to be positive, it may be assumed that the man threw off tubercle bacilli at intervals and constituted a probable source of infection. The diagram of the seating arrangement of the shop showed that the girl who had died had sat next to this man for one year. She had had no apparent contact with the other tuberculous workers in the shop.

Finding 8 definite cases of pulmonary tuberculosis, 4 of which were active, in one shop, is unusual in our experience. However, if such unusual situations can be discovered through follow-up of cases of open and active tuberculosis, it is well for industry to accept the responsibility for such case-finding procedure.

The most ideal tuberculosis control program ever developed among the garment workers Union was begun in June 1945 by the Knitting Industry Workers, and promises, if continued, to be the most effective method for controlling and eventually eliminating tuberculosis.

Practically every one of the 4,294 knitgoods workers were X-rayed, in cooperation with the Brooklyn Tuberculosis and Health Association, using paper plates. After reading the plates, 135 persons, an unusually large number, were called in for further study because their roentgenograms showed in each the presence of a lesion that might be considered suspicious of tuberculosis. In this instance an exceedingly high standard of procedure was developed because the U. S. Public Health Service became interested in utilizing this group as the basis for a research project. The purpose is to study, by frequent periodic X-ray examination, reactivation and changes in the character of the lesion that might occur during a five-year period.

Each patient visited the Union Health Center twice for a complete work-up. On the first visit a thorough physical examination, sedimentation rate, hemoglobin, Wassermann test, urinalysis, chest X-ray celluloid film and first-dose tuberculin test were done. A sputum bottle was given for collecting a specimen and on the second visit the sputum specimen was examined and gastric lavage was done.

The first phase of this survey resulted in the discovery of only one active case of tuberculosis. This member was hospitalized immediately and 76 members, or 1.7 per cent of the total membership, were selected for study over the five-year period.

The continuous character of this method of control gave us an opportunity late in October to survey 408 additional workers who entered the industry since the first survey in June. From these new members, 26 cases were called in for 14" x 17" celluloid films. Of the 26, one had moderately advanced pulmonary tuberculosis requiring hospitalization and 8 were considered to have X-ray findings that deserved further physical examination and diagnostic studies. Of these 8, 4 required periodic supervision to make sure their lesions were stabilized.

In 1939 this same Knitgoods workers group first surveyed 2,546 workers, 42 per cent of the membership, at which time 18 persons were found to have clinically significant findings and 8 members were discovered to be suffering from active pulmonary tuberculosis requiring hospitalization or sanatorium care.

It has been my experience with the unions whose health programs I administer that the extent of labor participation in the fight against this disease is paralleled by its economic strength. When medical and economic aid to sick members is available, excellent coöperation with tuberculosis programs may be assured.

A long range tuberculosis program sponsored by industry can be accomplished by:

1. Periodic surveys of industrial groups, at three-year intervals, at least.
2. X-ray examination every three to six months of all persons who enter the industry since last complete X-ray survey.
3. Provision of hospital or sanatorium care for all tuberculous workers.
4. Financial aid to the worker during disability and to the worker's dependents during this period.
5. Rehabilitation by the provision of an adequate number of sheltered work-shops, which would also take care of the custodial case.
6. Job placement for the stabilized tuberculous ex-patient.
7. Necessary medical supervision of questionable and inactive cases of tuberculosis as long as the patient works in industry, without cost to the patient.
8. Medical aid for workers whom X-ray examination reveals having other abnormality of the lungs, heart or chest.

The experience of the Union Health Center with Labor's efforts to control tuberculosis emphasizes the necessity for education—through mass X-ray surveys, through free physical examinations at a time and place acceptable to the worker—to arouse health consciousness. It has found that the more carefully tuberculosis is looked for, the more cases will be discovered. It knows that material aid for the tuberculous workers—economic as well as medical—can be effective in overcoming the worker's fear of having the disease discovered in himself. And we are convinced that the more funds are available for such a program, the more certainty there is that the fullest coöperation will be forthcoming.

It is pretty well recognized by the workers in this industry that the earlier tuberculosis is discovered the easier it is to cure. They accept the idea that the knowledge that a person is not afflicted with tuberculosis is important to his peace of mind. Coöperation with X-ray surveys to eradicate tuberculosis has become possible because reassurance can be given that the worker will receive medical and economic support. Management in the industry has made a great contribution by furnishing funds for the medical services and indemnities that are one of the most important phases of this program.

The problem of the control and ultimate eradication of tuberculosis is so complex and costly that full coöperation from every section of the community on a nation-wide scale is essential. The large industrial bulk of this nation must participate more and more in this fight to eliminate tuberculosis.

## SUMMARY

Tuberculosis as a "proletarian" disease deeply interests the average worker. But he often shuns tuberculosis-finding programs because he knows the discovery of the disease in himself means the loss of a job, hospitalization, impoverished dependents and trouble in finding work after the disease is stabilized.

One labor union has endeavored to supply medical and economic aid for its own members who are afflicted with the disease. The International Ladies Garment Workers Union (which now numbers 165,000 members in New York City) first established a tuberculosis insurance program in 1913.

During the first twelve years of the program, 35,000 union members were examined and 500 were found to be tuberculous; 36,000 candidates for union membership underwent examination and 40 persons with active tuberculosis were rejected. After the National Recovery Act in 1934, when the unions gained financial strength, laboratory and X-ray procedures could be utilized in tuberculosis-finding campaigns. In 1939 an X-ray survey of almost 24,000 garment workers was made and 57 persons (0.23 per cent) were found with active pulmonary tuberculosis.

Collective bargaining made it possible for the entire industry to undertake tuberculosis control. In 1942 union contracts first contained a clause requiring the employers to pay a tax on the payroll for health aids to employees. With these funds, improved medical service for garment workers became possible.

A long-range tuberculosis control program sponsored by industry should consist of periodic X-ray examinations, sanatorium care and financial aid for tuberculosis patients, rehabilitation in sheltered workshops and medical supervision of workers who have ever had tuberculosis. Members of the ILGWU cooperate with X-ray surveys to eradicate tuberculosis, because assurance can be given that the victims of this disease will receive medical and economic support.

## SUMARIO

La tuberculosis como enfermedad del "proletariado" interesa profundamente a la mayoría de los obreros, pero a menudo éstos evaden las obras de hallazgo de casos por saber que el descubrimiento de la enfermedad en una persona trae consigo la pérdida de empleo, hospitalización, empobrecimiento de la familia, y dificultad para encontrar trabajo después que se estabiliza el mal.

Una unión obrera se ha esforzado por facilitar ayuda médica y económica a los socios afectados por la enfermedad. La Unión Internacional de Trabajadores en Ropa de Mujer (que cuenta hoy día con unos 165,000 socios en la ciudad de Nueva York) inició en 1913 una obra de seguro antituberculoso.

Durante los primeros doce años, de 35,000 socios examinados, resultaron tuberculosos 500; también se examinó a 36,000 candidatos para entrada, rechazándose a 40 que tenían tuberculosis activa. Después de promulgada la Ley de Recuperación Nacional de 1934, que dió nuevo vigor conómico a las uniones obreras, pudieron utilizarse técnicas de laboratorio y de rayos X, en la campaña de descubrimiento de casos. En 1939 se hizo una encuesta radiográfica de casi

24,000 trabajadores en ropa, y en 57 (0.23%) se encontró tuberculosis pulmonar activa.

La organización colectiva ha capacitado a toda la industria para emprender la lucha antituberculosa. En 1942, los contratos de la unión contuvieron por primera vez, una cláusula que obligaba a los patronos a satisfacer un impuesto sobre el total de salarios, destinado a mantener la salud de los empleados, y con esos fondos fué posible mejorar el servicio médico prestado a los trabajadores.

Una obra de lucha antituberculosa de largo plazo, patrocinada por la industria, debe consistir en exámenes radiográficos periódicos, asistencia sanatorial y ayuda económica a los tuberculosos, rehabilitación en talleres protegidos, y vigilancia médica de todo obrero que haya tenido alguna vez tuberculosis. Los miembros de la unión cooperan en las encuestas radiográficas para erradicar la tuberculosis por poderseles dar la seguridad de que las víctimas del mal recibirán apoyo médico y económico.

# MASS MINIATURE RADIOGRAPHY

A Survey in the United States Army Air Forces

EDGAR WAYBURN<sup>1</sup>

From April to September, 1945 a mass X-ray survey of the chest was conducted on over 77,000 persons in the U. S. Army Air Forces in England by means of two mobile X-ray trailer units.<sup>2</sup> Thirty-five mm. photofluorographic units<sup>3</sup> were permanently installed in the central portion of Fruehauf semi-trailers, thirty feet long and eight feet wide, being arranged in series along one side. The rear seven feet of the trailer was separated by a lead partition for a dark room. This chamber was separated from the X-ray room by a lead wall. Electric power was generated by means of a large gasoline-driven power unit. In one mobile unit this was 35 KVA and located in the fore part of the trailer; in the other, 62.5 KVA and mounted on the pontoon of the cab which hauled the trailer. The mobile units were equipped to take both miniature and full-size X-ray films of the chest and to process both types. Interpretations were made in a central office where the films and records were kept. The miniature films were viewed by projection to a size of five inches square against a white paper screen.

A full account of the equipment, technical and administrative methods employed in the survey has been given in a special report to the Air Surgeon (1).

## RESULTS<sup>4</sup>

A total of 77,480 persons had miniature X-ray films of the chest made. Four hundred and sixty-six, or 0.6 per cent, of these were British civilians, American Red Cross workers and Royal Air Force personnel who worked intimately with the U. S. Air Forces, leaving a total of 77,016 military personnel. Confirmatory 14 by 17 inch chest films were made on 2.5 per cent of the persons examined. The diagnostic classification is shown in table 1.

*Type of population:* The information on the type of population in this survey has been obtained by punch card analysis of the total diagnoses of abnormalities and by selection of every tenth card among the normals (or diagnosis no. 1).

Of the persons examined, 99.2 per cent were male and the same percentage were members of the white race; 14.4 per cent were fliers and 85.6 per cent were non-flying personnel.

The age groups are shown in table 2. It may be noted that 73 per cent of the

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<sup>2</sup> Dr. Peter Kerley and Miss Kathleen Clark gave invaluable assistance in this work.

<sup>3</sup> The equipment for one unit was manufactured by Messrs. Kodak Ltd., and for the other by Messrs. Watson & Sons (Electro-Medical) Ltd.

<sup>4</sup> The statistical tests of significance used were the standard error of the difference of proportions and the chi square test. Differences of more than twice the standard error or a probability of less than five in one hundred were considered significant. Professor Bradford Hill kindly checked the calculations.

normals fall into the age group 21 to 30. Inasmuch as the normals dominate the survey, this can be taken as the general age distribution.

*Pulmonary tuberculosis:* As is shown in table 1, there were discovered 5 cases (0.006 per cent) of active pulmonary tuberculosis, primary type, and 65 (0.08 per cent) of active pulmonary tuberculosis, reinfection type, as well as 204 persons (0.26 per cent) with inactive reinfection type tuberculosis. The persons with reinfection type tuberculosis were compared with the normals and with those with all types of abnormalities (see below). In addition, lesions of healed primary infections were noted in the lung parenchyma of 4.38 per cent and calcified hilar lymph nodes in 3.97 per cent.

The rather large number of persons with more than one diagnosis is due to the fact that a healed primary complex with large calcified lymph nodes in the hilar regions may be recorded twice. Interest in this was roused because calcified hilar lymph nodes above a certain number and size were a cause of exemption from military service in the U. S. Army (2). However, their appearance is still widespread in this survey. Extensive hilar calcification seemed to have no relationship to the incidence of active reinfection type tuberculosis as judged from the small percentage of cases in which the two conditions coincided.

Among the cases diagnosed active reinfection type pulmonary tuberculosis 4 were far advanced, 10 moderately advanced and 51 minimal in extent of the lesions. In only 2 cases were tubercle bacilli demonstrated during the time of observation in hospitals in England, but more may well have been discovered on complete study after return to the United States since these patients were transferred as quickly as possible. The location of focal lesions among inactive and active reinfection type pulmonary tuberculosis is shown in table 3. The most interesting observations are the greater frequency with which bilateral disease is apparent in active as compared to inactive infection, and the rather high prevalence of healed disseminated lesions.

#### *Factors Influencing the Incidence of Pulmonary Tuberculosis*

Analyses of different factors have been made to determine whether or not they have any influence on the incidence of pulmonary tuberculosis in this group of examinees.

*Age:* The ages of the persons examined divided into five-year periods are shown in table 2 and portrayed graphically in graph 1. It is seen that the percentage of cases in the sample of normals and in the total number of pathological cases coincide in all age groups; on the other hand the curve of pulmonary tuberculosis begins to rise in an older age group. In the 31 to 35 and 36 to 40-year groups the percentage of cases of inactive pulmonary tuberculosis is significantly higher than the proportion of this age group to the total population among the normals. In the age group 36 to 40 the percentage of cases of active tuberculosis is three times as high as the percentage of this age group among normals. Analysis of the figures by the chi square test suggests that the differences are statistically significant. The increase in the prevalence of active disease in the older age groups is contrary to the formerly accepted view but has been observed

TABLE 1

*Diagnosis code list with number of times various chest conditions were encountered in United States Army Air Force personnel in England*

DIAGNOSIS	INCIDENCE	PERCENTAGE OF TOTAL EXAMINEES
1 Normal chest.....	69,666	90.46
2 Bone, congenital abnormality.....	676	0.87
3 Bone, acquired lesion.....	596	0.77
4 Cardiovascular lesions, congenital.....	17	0.02
a. Dextrocardia..... 9		(0.01)
5 Cardiovascular lesions, acquired.....	9	0.01
6 Diaphragm, abnormality.....	13	0.01
7 Pleura, scarring (including fibrosis).....	811	1.05
8 Pleura, effusion.....	7	0.009
9 Lymph nodes, calcified.....	3,062	3.97
10 Lymph nodes, noncalcified (enlarged).....	2	0.002
11 Mediastinum, enlargement.....	8	0.01
12 Neoplasm.....	2	0.002
13 Lung, congenital abnormality.....	51	0.06
14 Pneumothorax.....	2	0.002
15 Pneumonia, nontuberculous.....	49	0.06
16 Bronchiectasis.....	1	0.001
17 Lung abscess.....		
18 Emphysema.....	4	0.005
19 Atelectasis.....	1	0.001
20 Pneumonoconiosis.....	6	0.007
21 Pulmonary tuberculosis, primary, active.....	5	0.006
22 Pulmonary tuberculosis, primary, inactive.....	3,376	4.38
23 Pulmonary tuberculosis, reinfection, active.....	65	0.08
24 Pulmonary tuberculosis, reinfection, inactive.....	204	0.26
25 Diagnosis undetermined, location.....		
26 Miniature film missing.....		
27 Miniature film technically faulty.....	5	0.006
28 Large film missing.....		
29 Clinical examination missing.....		
30 Foreign body.....	40	0.05
31 Other.....	28	0.03
a. Sarcoidosis..... 7		(0.009)
b. Gynecomastia..... 5		(0.006)
c. Solitary pulmonary tumor..... 5		(0.006)
Total pathological diagnoses.....	8,994	
Total number of persons in whom abnormalities were found.....	7,350	9.54
Total.....	77,016	100.00

The percentages of sub-diagnoses, which are in parentheses, are also included in the corresponding major diagnoses.

recently in similar types of surveys in both the British Isles (3, 4, 5) and the United States (6).

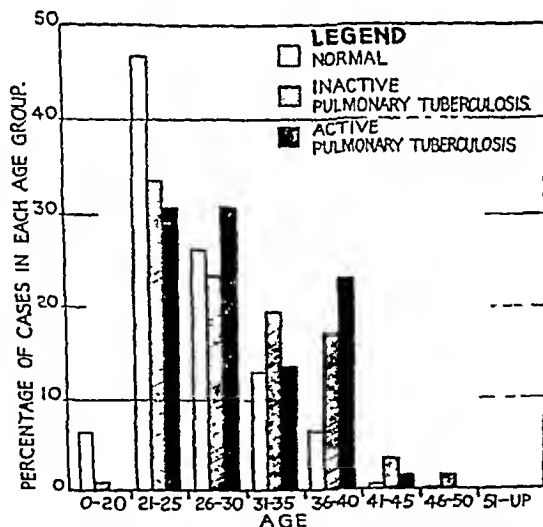


*Change of weight:* Table 4 and graph 2 show the curve of the change of weight of persons with pulmonary tuberculosis as compared with that of normals since entry into military service. It is seen that the curve for normals and the curve for inactive tuberculosis are similar. Most soldiers gained moderately in military

TABLE 2

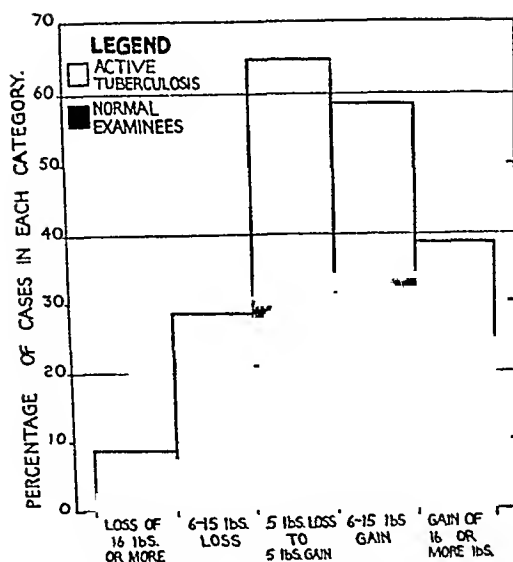
*Distribution of persons examined with normal and pathological chest findings, according to age, divided in five-year groups*

AGE GROUPS	NORMAL		ALL PATHOLOGICAL FINDINGS		INACTIVE PULMONARY TUBERCULOSIS		ACTIVE PULMONARY TUBERCULOSIS	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
20 and under	461	6.63	422	5.74	2	0.98	0	0.00
21-25	3,252	46.79	3,043	41.40	69	33.82	20	30.76
26-30	1,840	26.47	1,973	26.84	48	23.52	20	30.76
31-35	905	13.02	1,166	15.86	40	19.60	9	13.84
36-40	441	6.34	650	8.84	35	17.15	15	23.07
41-45	34	0.48	65	0.88	7	3.43	1	1.53
46-50	11	0.15	26	0.35	3	1.47	0	0.00
51 and up	5	0.07	5	0.06	0	0.00	0	0.00
Total.....	6,949	100.00	7,350	100.00	204	100.00	65	100.00



GRAPH 1. Comparison of normal and tuberculous persons examined, according to age, arranged in five-year groups.

service with the peak of change being reached among those who gained 6 to 10 pounds. On the other hand a much smaller percentage of persons with active pulmonary tuberculosis gained much or at all and a rather high percentage showed a moderate to considerable loss. Analysis by the chi square test sug-



GRAPH 2. Comparison of weight change in normal persons examined and those with pulmonary tuberculosis.

TABLE 3

*Location of lesions of pulmonary tuberculosis, reinfection type*

LOCATION	ACTIVE	INACTIVE
Bilateral.....	10	13
Right upper zone.....	28	74
Right middle zone.....	2	3
Right lower zone.....	4	5
Left upper zone.....	18	57
Left middle zone.....	1	3
Left lower.....	2	3
Disseminated.....	0	46
Total.....	65	204

TABLE 4

*Change in weight of normal persons examined and those with pulmonary tuberculosis*

WEIGHT	NORMAL		INACTIVE PULMONARY TUBERCULOSIS		ACTIVE PULMONARY TUBERCULOSIS	
	Number	Per cent	Number	Per cent	Number	Per cent
Loss of 16 pounds or more....	185	2.66	15	7.35	4	6.15
Loss of 6 to 15 pounds.....	517	7.42	17	8.33	14	21.53
5 pounds gain to 5 pounds loss..	2,156	31.00	65	31.86	22	33.84
Gain of 6 to 15 pounds.....	2,373	34.13	64	31.37	16	24.61
Gain of 16 pounds or more....	1,718	24.72	43	21.07	9	13.84
Total.....	6,949	100.00	204	100.0	65	100.00

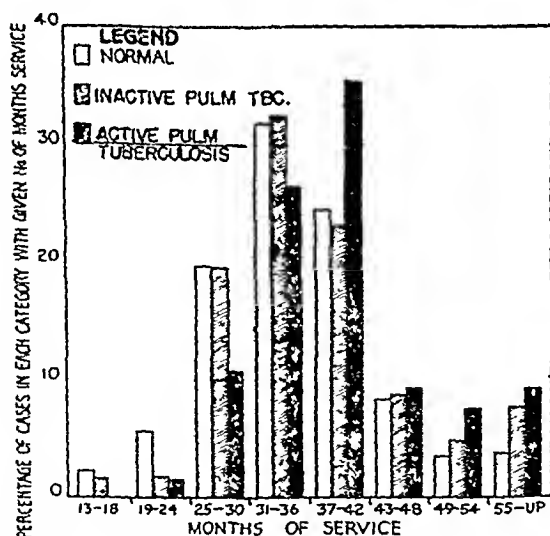
gests that this shift of the weight curve among asymptomatic persons with active pulmonary tuberculosis is statistically significant.

*Length of military service:* The duration of military service in the population

TABLE 5

*Number of months in military service of persons examined with normal and pathological chest findings, arranged in six months groups*

MONTHS	NORMAL		ALL PATHOLOGICAL FINDINGS		INACTIVE PULMONARY TUBERCULOSIS		ACTIVE PULMONARY TUBERCULOSIS	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Up to 12	24	0.34	36	0.489	0	0.00	0	0.00
13-18	154	2.21	163	2.217	3	1.47	0	0.00
19-24	398	5.73	626	8.517	4	1.96	1	1.53
25-30	1,378	19.83	1,505	20.47	40	19.60	7	10.77
31-36	2,209	31.78	2,143	29.15	66	32.35	17	26.15
37-42	1,690	24.32	1,688	22.96	47	23.03	23	35.38
43-48	576	8.29	595	8.09	18	8.82	6	9.23
49-54	254	3.65	297	4.04	10	4.90	5	7.69
55 up	266	3.85	297	4.04	16	7.84	6	9.23
Total... ..	6,949	100.00	7,350	100.00	204	100.00	65	100.00



GRAPH 3. Comparison of normal and tuberculous persons examined, according to length of military service.

surveyed is shown in table 5, and graphically portrayed in graph 3. The curve of the number of cases of active pulmonary tuberculosis in proportion to the total number of cases lags behind that of all other types of cases until the period of thirty-seven to forty-two months service. At this time it reaches a peak as

compared with the thirty-one to thirty-six-month peak of normals and total pathological cases. According to the chi square test the proportion of men with both active and inactive tuberculosis is significantly higher among men who have been in service for a period longer than the average. The cause of this may lie in one of several reasons. The first is that routine X-ray films of the chest of all the men entering the service were not made mandatory until thirty to thirty-six months before this survey, so that some of the persons involved were admitted to the Army despite the fact that they were affected with pulmonary tuberculosis which might have been detected by routine chest X-ray films. The second reason is that between thirty to thirty-six months had elapsed since the last X-ray film, whereas men coming into the service more recently had a more recent check. The third is the possible influence of service overseas.

*Length of service in European Theater of Operations:* The duration of military service in the European Theater, which for those examined means England, is shown in table 6 and portrayed in graph 4. This curve is similar to that of the total duration of service. The percentage of the total number of cases of active pulmonary tuberculosis is relatively higher among men who have been overseas thirty-one to forty-two months, as is apparent from a comparison of the curves in graph 4. Inasmuch as the men who have been overseas for the longest period are in general men who have been in military service the longest, it is probable that the same factor is responsible for both. Analyses by the chi square test suggest that the differences between cases of active tuberculosis and normals are statistically significant, although those between inactive tuberculosis and normals are within the limit of chance.

*Flying personnel:* A common impression without statistical backing has been that flying is responsible for an increased occurrence of pulmonary tuberculosis. This is not borne out by the prevalence of pulmonary tuberculosis in the present series. Whereas flying personnel composed 14.4 per cent of the total personnel surveyed, the incidence of fliers among cases of inactive pulmonary tuberculosis was 6.9 per cent and among cases of active pulmonary tuberculosis 3.1 per cent (table 7, graph 5).

It is of interest that most of the flying personnel had been overseas a much shorter length of time than the ground personnel and in general had been examined more recently. In other words, the fact that tuberculosis occurred much less frequently among flying personnel was due to a more rigid preselection for this type of work.

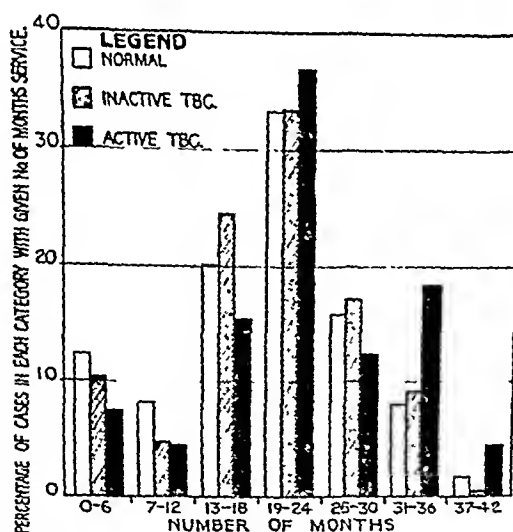
*Previous history:* An attempt was made to obtain information on certain miscellaneous items which were thought to be of interest in connection with the prevalence of pulmonary tuberculosis. The questions were asked before the men were examined but by comparatively untrained clerks so that the results are not necessarily accurate. They are recorded briefly because there was a pronounced difference in the results among the normals and the cases of tuberculosis. A history of pulmonary disease at sometime in the past was obtained from 4.6 per cent of those with active tuberculosis and 11.8 per cent of those with inactive tuberculosis, whereas only 1.3 per cent of the normal persons gave such a

history. It is suggested that individuals with inactive tuberculosis may be more aware of pulmonary disease than most others. Of the patients with active tuberculosis, 12.3 per cent admitted to known contact with tuberculosis as compared

TABLE 6

*Number of months service in European theater of operations of persons examined with normal and pathological chest findings, arranged in six months groups*

MONTHS	NORMAL		ALL PATHOLOGICAL FINDINGS		INACTIVE PULMONARY TUBERCULOSIS		ACTIVE PULMONARY TUBERCULOSIS	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
0-6	852	12.26	908	12.35	21	10.29	5	7.69
7-12	582	8.37	645	8.77	10	4.90	3	4.61
13-18	1,392	20.03	1,411	19.19	50	24.50	10	15.38
19-24	2,314	33.29	2,358	32.08	68	33.33	24	36.92
25-30	1,107	15.93	1,127	15.33	35	17.15	8	12.30
31-36	564	8.11	756	10.28	19	9.31	12	18.46
37-42	125	1.79	142	1.93	1	0.49	3	4.61
43-48	0	0.00	2	0.02	0	0.00	0	0.00
49 up	13	0.02	1	0.01	0	0.00	0	0.00
Total.....	6,949	100.00	7,350	100.00	204	100.00	65	100.00



GRAPH 4. Comparison of normal and tuberculous persons examined, according to number of months service in European Theater of Operations.

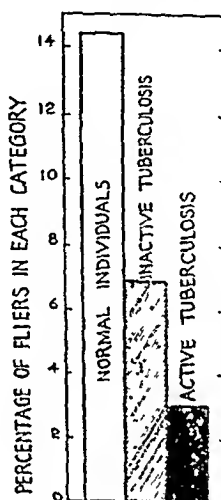
with a similar history in 8.3 per cent of those with inactive tuberculosis and 3.6 per cent of the normals.

*History and X-ray in European Theater of Operations:* There was no difference in the number of times ill since coming to the European Theater of Operations

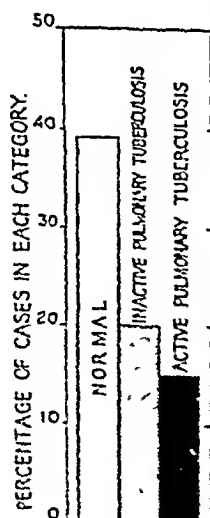
TABLE 7

*Incidence of pulmonary tuberculosis among flying and non-flying personnel*

CATEGORY	NORMAL		INACTIVE PULMONARY TUBERCULOSIS		ACTIVE PULMONARY TUBERCULOSIS	
	Number	Per cent	Number	Per cent	Number	Per cent
Flier .....	1,002	14.41	14	6.86	2	3.07
Non-flier .....	5,947	85.53	190	93.13	63	96.92
Total .....	6,949	100.00	204	100.00	65	100.00



GRAPH 5. Incidence of pulmonary tuberculosis among flying personnel.



GRAPH 6. Comparison of normal and tuberculous persons examined, with regard to previous X-ray examination of chest in European Theater of Operations.

among the men in whom tuberculosis was discovered and the normals. An interesting observation is that only 15.4 per cent of the men with active tuberculosis and 20 per cent of those with inactive disease had had a previous X-ray film of the chest in the European Theater of Operations, compared with 39 per cent of the normals (graph 6). The obvious corollary to this observation is that periodic chest films would pick up these lesions earlier.

*Local milk consumption:* At the beginning of this survey it had been suggested that the consumption of local, unpasteurized milk from cows that were not tested with tuberculin might be responsible for an increased incidence of tuberculosis among the troops in this area. Inquiry was made of all men with regard to the consumption of milk. The answers to the query suggest that approximately 38 per cent of both normals and persons with inactive tuberculosis consumed some local milk, whereas approximately 54 per cent of those with active tuberculosis did so. Since no further information on this point is available, no conclusion is drawn although it seems possible that the longer a person remained in the local community the more likely he would be to consume the milk, and that the answers to the question may be correlated to the duration of foreign service.

*Nontuberculous lesions:* Numerous conditions of the chest other than tuberculosis were found, as enumerated in table 1. A large part of the acquired lesions of bones was scoliosis of moderate to marked degree, in 0.77 per cent. A number of instances of fatigue fracture of the first rib described by Alderson (7) and others were included in this category.

The incidence of nontuberculous conditions of the lung included 51 cases of azygos lobe, 49 of nontuberculous pneumonia, 6 of pneumoconiosis, 4 of emphysema, 2 of spontaneous pneumothorax, one of bronchiectasis and one of massive atelectasis. There were 7 cases presumed to be pulmonary sarcoidosis, only one of which had had symptoms, and 5 cases of a soft spheroid shadow in the posterior portion of the right lower lobe, associated in 4 instances with an anomaly of the rib. This last group of cases is described more fully in a separate paper (16).

#### DISCUSSION

*General:* A mass chest X-ray survey has been completed rapidly over a considerable territory in a number of different locations by two completely mobile photo-X-ray units. While the methods used have been most easy to utilize in military service it is felt that the principles can be applied to civilian life, with favorable publicity and good organization as the media to substitute for military orders in getting sufficient numbers of any group together at any time. A number of completely mobile units are in operation or in prospect in the United States; two are in use in Great Britain; several have been used by the German military services; one is at work in Sweden. The clinical results of the work of these various units are not known to the author. It is envisaged that in the near future it will be possible to examine all military personnel in dispersed camps at fairly frequent intervals.

*Apparatus:* To accomplish successfully a large scale mass radiographic survey

requires a number of coördinated factors. The radiographic apparatus should be of a type adapted for mass work as distinct from all other types of field or hospital roentgenology. It must be able to endure a large number of exposures daily week after week, month after month. It must be able to take successfully variations in electric current and without breakdown. It must be able to photograph the entire chest of a large man. Several X-ray companies in Europe and a number in the United States are now manufacturing equipment which is suitable from these various angles. The present survey has been performed with 35 mm. apparatus. Such equipment is durable and efficient and, when operated by skilled technicians, is capable of producing films of high diagnostic quality.

*Mobility:* A special and desirable feature of this survey has been the complete mobility of the field units, which were planned so that they could go to any military installment in the United Kingdom. To accomplish this, sturdy rolling stock and sturdy roentgen-fluorographic equipment permanently installed in a vehicle have been essential. It is considered that this is superior to equipment transported in small vans and moved in and out of a building at each stop, although this procedure has been serviceable under conditions which involve less frequent moves, and these to larger places (8).

*Value and accuracy of 35 mm. films:* The primary use of a survey with 35 mm. film is to provide a screen through which to sift a great number of apparently normal people and to pick from this large number a smaller group in whom the chest film suggests possible lesions. With the 35 mm. apparatus a large number of films can be taken very speedily at a minimum cost. It also enables the interpreter to view easily a much larger number of films in a shorter period of time than he could were conventional 14 by 17 inch films used. Thirty-five mm. photofluorography is not a substitute for large film roentgenography. The detail and accurate localization of lesions possible in the latter can never be reached in the former. However, it may be said emphatically that a good miniature film is preferable to a poor large film.

The enlargement of pulmonary lesions produced by the close tube-screen distance at which the miniature films are taken, the additional contrast and the concentration of the rays on the small film area result in a picture which is frequently more obvious and consequently easier to see at first glance than on the large film.

In a recent comparative analysis of 35 mm. with stereoscopic 4 by 10 inch film, 14 by 17 inch film and 14 by 17 inch paper, Chamberlain (9) found that the 35 mm. technique was as efficient as any of the others. Skilled radiologists will miss some lesions on any size of film. In this survey a few lesions discovered on 35 mm. photoroentgenograms were later overlooked on 14 by 17 inch films. Conversely, coinciding with the experience of Chamberlain and with the informal opinion of many others the over-reading common in the interpretation of 35 mm. films may lead to positive reports which cannot be confirmed by the 14 by 17 inch check-up film.

*The importance of reexamination:* The low prevalence of active pulmonary



tuberculosis may be anticipated as a point against the cost of a survey such as this one from the economic aspect. In this regard it may be stated that the number of cases of active tuberculosis removed from the body of the population will result in a saving to the government of a sum many times that of the cost of the survey. The number of potentially tuberculous individuals removed from contact with the active cases adds greatly to this. Beginning treatment at an earlier stage likewise lessens the monetary cost of the disease in the individuals affected.

The U. S. Army has had facilities for routine chest X-ray films since 1941. Between 0.9 per cent and 2.0 per cent of selectees were rejected on the basis of pulmonary tuberculosis (10, 11, 12, 13, 14, 15) and a much smaller percentage for nontuberculous lesions or deformities of the chest. This survey represents the reexamination of men previously screened.

All of the figures which appear significant in the analyses of the present survey seem to point towards the argument that the more frequently routine X-ray examination of the chest is made, the lower will be the percentage of active pulmonary tuberculosis among a given population. Towards this conclusion are adduced the statistics suggesting that there is a significant increase in the percentage of cases of tuberculosis among men who have been longer in military service (that is, longer since the X-ray examination at induction) and among men who have been longer overseas. It should be added that the latter increase is not as great as the former and that there is no statistical evidence that such factors as the English climate, the consumption of local milk or exposure to the local population (except in specific instances of exposure) have caused an increase in the incidence of tuberculosis.

The great majority of all persons examined had had a chest film on induction and 10 out of the 65 with active disease had been examined by X-ray previously in this Theater. Active lesions were discovered in persons who had had a normal chest film as short a time as two months prior. The ideal interval between chest examinations for the apparently normal subject cannot yet be stated accurately, but a film each year, similar to the periodic dental examination, is certainly desirable.

#### SUMMARY AND CONCLUSIONS

Two mass miniature (35 mm.) radiographic units were permanently installed in large semi-trailers with specially designed interiors. During the course of five months 77,480 persons in 49 different stations were examined. The personnel were preselected in that they were young men in military service, on foreign duty, living under barracks conditions in the U. S. Army Air Forces, and, largely, had been examined within three years previously.

In this population there were found 0.006 per cent of active primary pulmonary tuberculosis, 0.08 per cent of active reinfection type pulmonary tuberculosis and 0.26 per cent of healed reinfection type pulmonary tuberculosis.

Analyses of the results of the survey suggest that reinfection type active pulmonary tuberculosis occurred more frequently than is usually postulated in the 36 to 40 age group. The best method for the detection of reinfection type

pulmonary tuberculosis in an early stage is the routine periodic chest X-ray examination of apparently healthy persons.

There is nothing in the present survey to suggest that flying predisposes to pulmonary tuberculosis in previously healthy young men. Nor is there any evidence that the healed primary complex predisposes to active disease.

Active tuberculosis seems to occur more frequently in bilateral than in unilateral lesions.

Chest conditions of clinical interest other than tuberculosis were found in a total of 76 cases.

Routine mass chest radiographic surveys, by means of miniature films, furnish an accurate method of case-finding in tuberculosis and for the recognition of other conditions of the chest. Thirty-five millimeter photofluorography is the most economical and rapid technique and it is easily adaptable for mobile work.

#### SUMARIO Y CONCLUSIONES

Dos unidades destinadas a obtener radiografías en miniatura (35 mm.) en masa fueron instaladas permanentemente en grandes semicamiones (remolcados) de interior diseñado *ad hoc*. En un período de cinco meses, se examinó a 77,480 personas en 49 paradas distintas. El personal examinado había sido preseleccionado, tratándose de jóvenes en el servicio militar, en país extranjero, que vivían en cuarteles de las Fuerzas Aéreas del Ejército de E. U. A., y en gran parte, examinados tres años antes.

En esa población encontráronse: 0.006 por ciento de tuberculosis pulmonar primaria activa, 0.08 por ciento de tuberculosis pulmonar activa tipo reinfección y 0.26 por ciento de tuberculosis pulmonar curada tipo reinfección.

Los análisis del resultado de la encuesta indican que la tuberculosis pulmonar activa tipo reinfección fué más frecuente que lo que se suele considerar en el grupo de 36 a 40 años de edad. El método mejor para descubrir el tipo reinfección en el período incipiente consiste en el examen roentgenográfico periódico del tórax de las personas aparentemente sanas.

La encuesta no aportó dato alguno indicativo de que el vuelo predisponga a la tuberculosis pulmonar a los jóvenes previamente sanos, ni tampoco prueba alguna de que el complejo primario curado predisponga a la enfermedad activa.

La tuberculosis activa parece presentarse más a menudo en las lesiones bilaterales que en las unilaterales.

En 76 casos en conjunto encontráronse estados torácicos de valor clínico, aparte de tuberculosis.

Las encuestas radiográficas colectivas del tórax, por medio de películas en miniatura ofrecen una técnica exacta para el descubrimiento de casos de tuberculosis y el reconocimiento de otros estados torácicos. Las fotorroentgenografías de 35 mm. representan la técnica más rápida y económica, prestándose fácilmente para obras móviles.

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## SERIAL TUBERCULIN TESTS AND STABILITY OF THE TUBERCULIN REACTION<sup>1,2,3</sup>

RUTH R. PUFFER, H. C. STEWART, R. S. GASS AND E. F. HARRISON

The discovery of sensitivity to histoplasmin in children who have calcifications in the lung fields and fail to react to tuberculin (1) opens up a new field of research of clinical and public health value. Pathological and clinical evidence, according to Christie and Dawson of Vanderbilt (2), has shown that there may be a benign form of histoplasmosis causing calcifications in the lung. These recent studies indicate the need for investigation of other agents and of their differentiation from tuberculosis as a causative agent in producing pulmonary calcification. Such a differentiation requires consideration of the stability of sensitivity to tuberculin. Reversal from the tuberculin-positive to the tuberculin-negative state has been noted by many workers. Exact data, however, regarding the frequency of reversal according to degree of reaction and dosage are limited. The finding of calcification in a person tuberculin-negative was formerly thought to indicate loss of sensitivity to tuberculin. Thus, the discovery that agents other than the tubercle bacillus may be responsible for calcifications in the lung fields results in confusion in the literature on this subject. For clarification of this problem, data regarding the stability of the tuberculin reactions from serial tuberculin tests of school children are presented.

Data have accumulated in Williamson County as the result of 5 school surveys at two-year intervals. For the study of the tuberculin reaction, it is desirable to have, first, a short summary of the tuberculin testing program and the results of tuberculin tests in the 5 school surveys. A change in the percentage of the school children reacting to tuberculin over a period of time should be considered in the interpretation of data regarding the stability of the tuberculin reaction.

The first school survey was undertaken in 1937 to learn the prevalence of tuberculous infection and to understand the significance of calcium deposits in the lung fields. Although school surveys usually are limited to X-ray examinations of children with positive tuberculin tests, for this research it was agreed to make X-ray examinations of all children, in addition to tuberculin testing, in the large schools of the county having electric current. The clinicians read the films without knowledge of the results of tuberculin tests. The results reported in 1938 (3) indicated that definite calcified lesions were found nearly as frequently in white children tuberculin-negative (48.1 per cent) as in those tuberculin-positive (51.1 per cent).

To obtain additional information regarding this unexpected observation, school surveys were repeated at two-year intervals in 1939, 1941 and 1943. A

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review of serial films reported in 1943 (4) revealed that 83 per cent of the white children and 72 per cent of the colored children had calcified nodules in the lung fields and/or tracheobronchial calcification. Only 40.3 per cent of these white children with serial films and 45.4 per cent of the colored children had positive tuberculin reactions to 1.0 mg. Thus, an unusual situation existed in this area, with children with calcifications found far more frequently than children with positive reactions to tuberculin.

This discovery of excessive prevalence of pulmonary calcification, and particularly in children who were not sensitive to tuberculin, was followed by investigations in this field by other workers. Lumsden and Dearing (5) found a lack of correlation between calcification in the lung and allergy to tuberculin. Olson, Wright and Nolan (6) studied the relationship between pulmonary calcification and exposure to tuberculosis, ascariasis and other specific diseases. Cox and Smith (7) in California found that primary pulmonary calcification was produced by infection with *Coccidioides immitis*. Recently, Christie and Peterson (1) reported their investigation regarding pulmonary calcification in children negative to tuberculin and concluded: "A study of the chest roentgenograms and the skin sensitivity to histoplasmin and tuberculin of 181 children from middle Tennessee suggests an immunologic relationship between histoplasmin sensitivity and the problem of pulmonary calcification." From studies of tuberculin and histoplasmin tests and chest roentgenograms, Palmer (8) concludes "that a very high proportion of the pulmonary calcifications observed in roentgenograms of tuberculin negative persons is due, not to tuberculosis, but probably to histoplasmosis."

The fifth school survey in Williamson County in 1945 included skin testing with histoplasmin in addition to testing with tuberculin and X-ray examinations. At this time, the necessity of the investigation and possible differentiation of calcification due to tuberculosis and to other organisms makes it desirable that the stability of sensitivity to tuberculin be known. This paper reports the results of tuberculin tests in the 5 surveys of school children in Williamson County and the results of serial tuberculin tests on the children who were tested 2, 3, 4 or 5 times. The results of testing with histoplasmin will be reported later.

The question has been raised as to whether or not tuberculin allergy may disappear after complete healing of the lesion and whether reinfections from subsequent exposures are necessary for persistence of the original allergy. Dahlstrom (9) has raised these questions and has reported the results of tuberculin tests on 2,828 persons included in the files of the Henry Phipps Institute. His summary is of interest: "Of the group examined, 2,490 were positive to tuberculin in at least one examination, and 276 or 11.1 per cent of these passed from the positive to the negative state during the period of observation in the dispensary. The lower the original degree of sensitiveness was, the greater was the likelihood of reversal from a positive to a negative reaction. Only 0.4 per cent of 1,090 people giving a three-plus reaction to the standard first dose of tuberculin became tuberculin-negative whereas the negative state supervened in 70 per cent of 185 persons giving only a one-plus reaction to the second dose."

The question of the stability of the tuberculin reaction has been raised by other investigators. Only studies in which a series of tuberculin tests is used will be of value in discussing changes from the positive to the negative state. Investigations by Tortone and associates (10), Paretzky (11) and Lloyd and MacPherson (12) in which such changes have been directly observed are available. Rich (13) has summarized this literature and states that a negative tuberculin test is no proof that the individual has never been infected. Wells and Flahiff (14) found that between 25 and 30 per cent of the persons vaccinated with heat-killed tubercle bacilli who became positive and were retested thirteen to twenty-four months following vaccination lost sensitivity. The data in many reports are limited and frequently the degree of reaction was not included. It is of interest that in animal experimental work the reversion from tuberculin-positive to tuberculin-negative has been observed in guinea pigs. Willis (15) concludes from these studies: "After infection with tubercle bacilli of low virulence, guinea pigs exhibit a gradually declining cutaneous allergy as the infection subsides. At two years after infection they failed to react to twice the usual reactive dose of tuberculin."

#### RESULTS OF TUBERCULIN TESTS IN FIVE SCHOOL SURVEYS

In the 5 school surveys in 1937, 1939, 1941, 1943 and 1945, 5,828 tuberculin tests were completed on white children and 1,478 on colored children. The procedure followed was to give 0.01 mg. of Old Tuberculin and, if the reaction

TABLE 1

*Results of tuberculin tests in five school surveys at two-year intervals 1937-1945 by color*

YEAR	WHITE								COLORED							
	Total tested	Total positive		Positive to 0.01 mg.		Positive to 1.0 mg.		Total tested	Total positive		Positive to 0.01 mg.		Positive to 1.0 mg.		Total tested	Total positive
		Number	Per cent	Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent	Number	Per cent		
Total...	5,828	2,104	36.1	462	7.9	1,642	28.2	1,478	612	41.4	250	16.9	362	24.5		
1937	1,015	452	44.5	84	8.3	368	36.3	283	145	51.2	49	17.3	96	33.9		
1939	1,143	457	40.0	84	7.3	373	32.6	297	114	38.4	43	14.5	71	23.9		
1941	1,224	424	34.6	118	9.6	306	25.0	269	115	42.8	53	19.7	62	23.0		
1943	1,156	369	31.9	93	8.0	276	23.9	272	117	43.0	62	22.8	55	20.2		
1945	1,290	402	31.2	83	6.4	319	24.7	357	121	33.9	43	12.0	78	21.8		

was negative forty-eight hours later, to give a second dose of 1.0 mg. The same lot of Old Tuberculin has been used throughout this study in order to insure comparability of results. This lot was tested a little over two years ago by the United States Public Health Service against their lot of dried PPD. Specialists agree that it is doubtful that this lot of concentrated Old Tuberculin preserved with glycerine would have deteriorated since this last testing for potency in 1943.

The results of the tests by year are given in table 1.

A difference in the reactions to tuberculin by years was noted. Of the 5,828 completed tuberculin tests of white children, positive reactions to 0.01 mg. were read for 462, or 7.9 per cent. The percentages of tests positive to this small dose varied by years without showing any significant trend in this period. The proportion positive in 1945 (6.4 per cent), however, was slightly lower than the proportions in previous years. To the second dose (1.0 mg.) there were 1,612 positive tests. A decline in reactors to this dose was noted during the period from 36.3 per cent in 1937 to approximately 25 per cent in the last 3 surveys in 1941, 1943 and 1945. The proportion positive to both doses of tuberculin (31.2 per cent) in 1945 was lower than the proportion in 1937 (44.5 per cent).

Although the numbers are smaller in the colored group, the same differences were noted; namely, variation in the proportions reacting to 0.01 mg. with the lowest percentage in 1945 and a decline in the total reactors to tuberculin from 51.2 per cent in 1937 to 33.9 per cent in 1945.

The reactions of the colored school children to the two doses of tuberculin differed from those of white children. The proportion of colored children positive to the first test (16.9 per cent) was over twice the proportion of white children positive to the first test (7.9 per cent). This difference in the two racial groups has been noted by others (16). In the tuberculin testing program of 51,818 high school students in Tennessee (17) 13.3 per cent of the white and 28.4 per cent of the colored children reacted to 0.01 mg. of tuberculin. Aronson (18) noted a similar difference in the results of tuberculin testing in the two racial groups. Including tests with 0.01 mg. and 1.0 mg. in the Williamson County data, the percentage of colored children positive was 41.4, while the comparable percentage of white children was 36.1. The difference in the reactions to tuberculin in the two racial groups was principally in degree of reaction rather than in proportion of reactors. After infection with the tubercle bacillus, the colored child appears to show greater sensitivity. According to Rich (13), "The negro with his lower native resistance to tuberculosis develops a higher degree of hypersensitivity during infection than does the white." In discussing the mechanism of acquired resistance, however, he states, "The lack of parallelism between the degree of hypersensitivity and of acquired resistance is particularly striking in the negro."

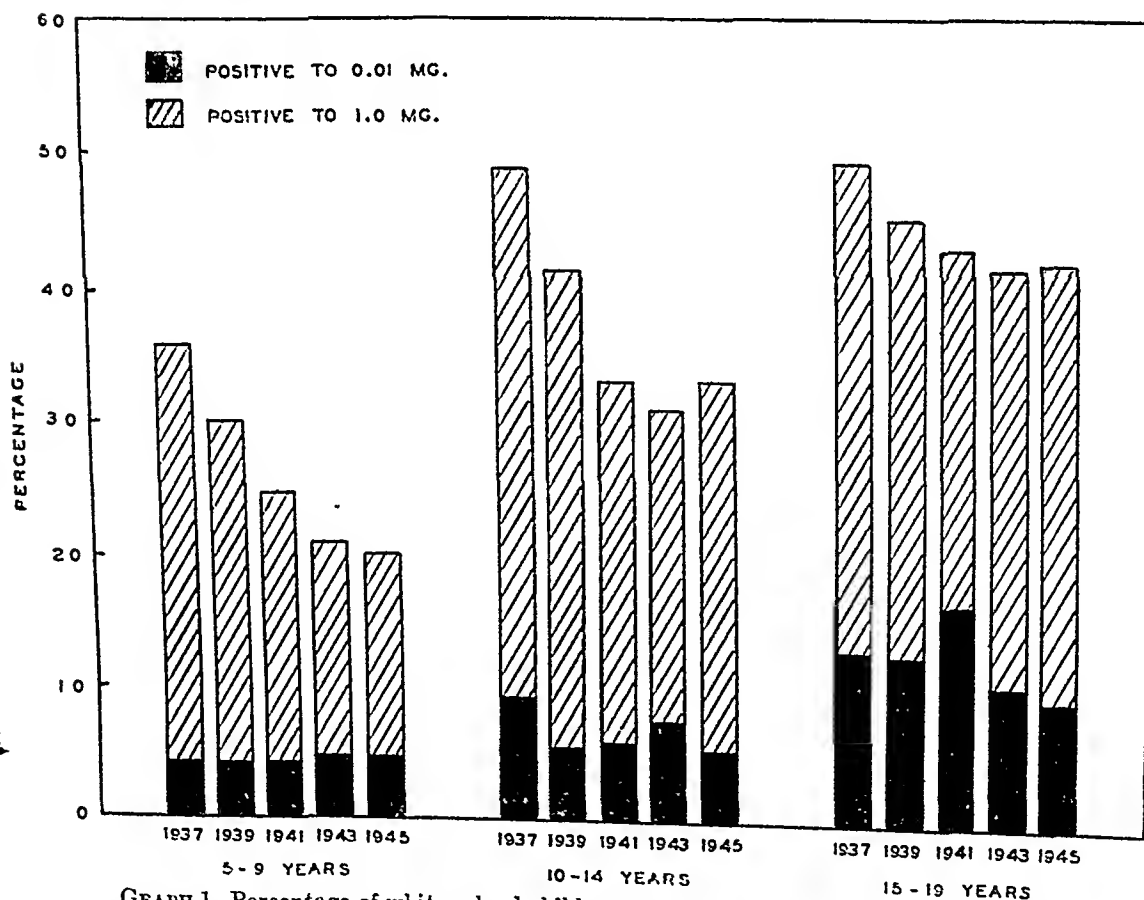
The material for the white school children is presented for three five-year age groups in table 2 and shown graphically in graph 1. Similar data for the colored children will not be presented because of the small number of children included in some of the groups.

The reduction in sensitivity to tuberculin appeared to be less for the older children than for the younger. While in 1937, 35.8 per cent of school children 5 to 9 years of age reacted to tuberculin, in 1945, only 20.0 per cent reacted—a 44 per cent reduction. Of the children in the oldest age group, 49.4 per cent reacted to tuberculin in 1937 and 41.8 per cent in 1945—a 15 per cent reduction. During this period of time a decline in the tuberculosis death rate in Williamson County has been noted (graph 2). For the five-year period 1935 to 1939 the average white tuberculosis death rate was 62.0 per 100,000 population and for the period 1940 to 1944 it was 23 per cent lower, 48.0 per 100,000 population.

TABLE 2

Results of tuberculin tests of white school children in three age groups in five school surveys 1937-1945

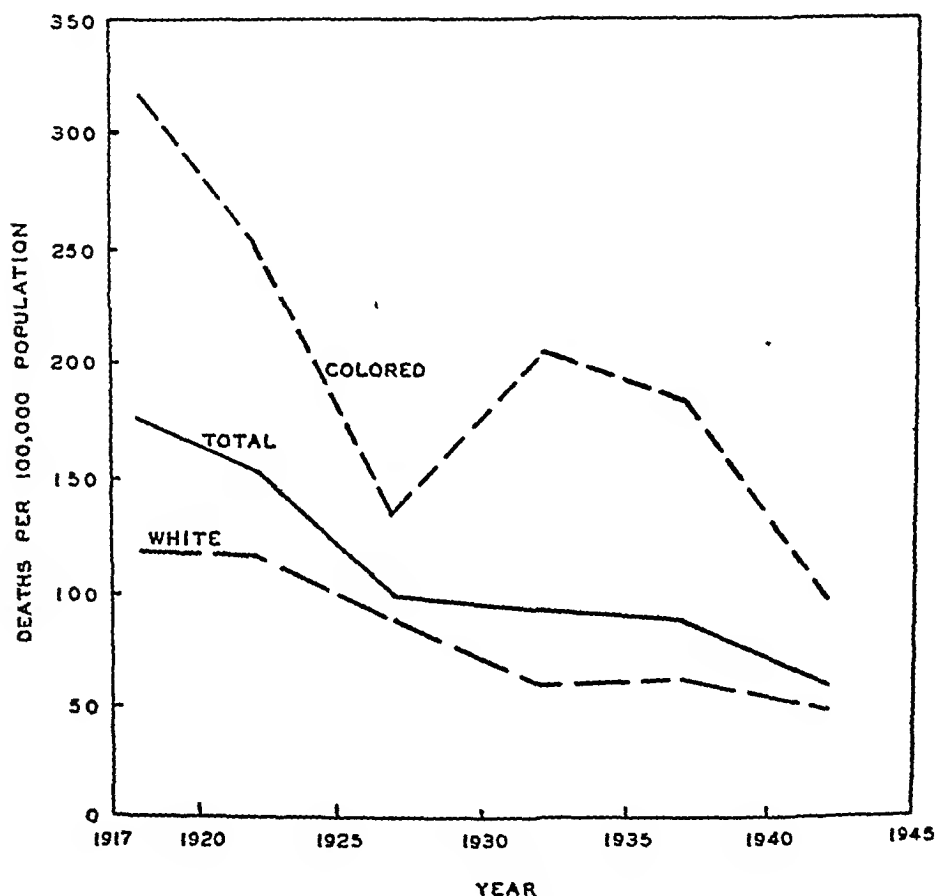
YEAR	5-9 YEARS					10-14 YEARS					15-19 YEARS				
	Total tested	Total positive		Positive to 0.01 mg.		Total tested	Total positive		Positive to 0.01 mg.		Total tested	Total positive		Positive to 0.01 mg.	
		Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent
Total..	1,660	437	26.3	72	4.3	2,439	909	37.3	168	6.9	1,729	758	43.8	222	12.8
1937	338	121	35.8	14	4.1	430	209	48.6	38	8.8	247	122	49.4	32	13.0
1939	321	98	30.5	13	4.0	467	197	42.2	26	5.6	355	162	45.6	45	12.7
1941	296	73	24.7	12	4.1	484	161	33.3	32	6.6	444	190	42.8	74	16.7
1943	291	62	21.3	14	4.8	505	158	31.3	39	7.7	360	149	41.4	40	11.1
1945	414	83	20.0	19	4.6	553	184	33.3	33	6.0	223	135	41.8	31	9.6



GRAPH 1. Percentage of white school children reacting to tuberculin, by age groups, at two-year intervals, 1937-1945 Williamson County Tuberculosis Study.



The decline in the colored tuberculosis death rate was even greater from 184.6 for 1935 to 1939 to 98.3 per 100,000 population for 1940 to 1944. With a declining tuberculosis death rate, the opportunities for exposure to tubercle bacilli would be reduced and a decline in reactors to tuberculin would be expected. Also a greater reduction would be noted for the younger children.



GRAPH 2. Tuberculosis death rates per 100,000 populations, by color, for Williamson County Tennessee, five-year averages 1917-1944.

#### RESULTS OF SERIAL TUBERCULIN TESTS

During these 5 school surveys, there were 1,482 white children and 339 colored children who had two or more tuberculin tests at intervals of two, four, six and eight years. The results of the first and last tests will be used in considering the stability of the tuberculin reaction. For the white children the average interval between first and last test was 3.9 years and for colored children 4.0 years.

The results of the first and last tests of white children will be considered first (table 3). Of the 1,482 children in this group, 93 reacted to 0.01 mg. of Old Tuberculin at the time of the first test. Since the number reacting to 1.0 mg.,

450, was large and three-fourths of the children showed only a one-plus reaction,<sup>4</sup> the results are presented in two groups, (a) those with two- and three-plus reactions to 1.0 mg. (107 children) and (b) those with one-plus reactions (343 children). Nine hundred and thirty-nine children did not react to 1.0 mg. of Old Tuberculin at the time of this first test.

Sensitivity to the first dose of tuberculin appeared to be relatively stable. Of 93 white children reacting to 0.01 mg., 77, or 82.8 per cent, were positive to 0.01 mg. at the last tuberculin test also. Six (6.5 per cent) showed a slightly less severe reaction, that is, a two- or three-plus to 1.0 mg.; 5 (5.4 per cent) showed only a one-plus reaction to 1.0 and 5 (5.4 per cent) were negative to 1.0 mg. Thus, only 5.4 per cent appeared to lose sensitivity, as measured by these two doses of tuberculin.

The loss of sensitivity to the second dose of tuberculin was considerably greater. Of the 107 children having a two- or three-plus reaction at the time of first test,

TABLE 3

*Results of last tuberculin test in relation to first tuberculin test of white school children*

FIRST TUBERCULIN TEST	TOTAL		LAST TUBERCULIN TEST							
			Positive to 0.01 mg.		Reaction to 1.0 mg.					
	Number	Per cent			+++ and ++		+		Negative	
			Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Total.....	1,482	100.0	159	10.7	139	9.4	273	18.4	911	61.5
Positive to 0.01 mg.	93	100.1	77	82.8	6	6.5	5	5.4	5	5.4
Reaction to 1.0 mg.										
+++ and ++	107	100.0	23	21.5	32	29.9	27	25.2	25	23.4
+	343	100.0	25	7.3	54	15.7	105	30.6	159	46.4
Negative	939	100.0	34	3.6	47	5.0	136	14.5	722	76.9

25, or 23.4 per cent, were negative to 1.0 mg. at the last test. Nearly half of those having a one-plus reaction to 1.0 mg. (46.4 per cent) were negative to 1.0 mg. at the last test. Of these having a one-plus reaction, 79, or 23.0 per cent, had a more severe reaction on the final test. This percentage was considerably higher than the percentage (8.6) of children with negative reactions on the first test having a two- or three-plus reaction on final test. It was, however, approximately the same as the percentage of the children with negative reactions becoming positive with any degree of sensitivity (23.1 per cent).

The results from serial tests of 339 colored school children were similar to those

<sup>4</sup>In these school surveys the tests were read according to degree or extent of the reaction. An area of edema surrounding the infection site of as much as 5 but less than 10 mm. in greatest diameter was read one-plus. Edema measuring 10 or more but less than 15 mm. in greatest diameter was read two-plus. Edema of 15 or more mm. in diameter was called three-plus. Any reaction, regardless of size, which resulted in necrosis was classed as a four-plus reaction.

of white school children (table 4). Of the colored children positive to 0.01 mg. on first test, 5.9 per cent were negative on the last test; of those two-, three- and four-plus to 1.0 mg. on first test, 28.0 per cent were negative on the last test; and of those one-plus to 1.0 mg., 43.5 per cent were negative on the last test.

Detailed information regarding the results of the tests on the 30 white children and 10 colored children who showed a two-plus or greater reaction to 1.0 mg. and were negative on the last test is given in table 5.

The results of the first tuberculin tests and the age of the children at the time of these first tests are given in table 5. The results of all subsequent tests are also shown. For only one child in this series were five tests completed. For this child a variability in sensitivity was noted with the final test negative. Sixteen of these children who showed a reversion to the negative state had their final test six years after their initial test. These children could have had their original tests in either 1937 or 1939. For 3 of these children, variability in re-

TABLE 4

*Results of last tuberculin test in relation to first tuberculin test of colored school children*

FIRST TUBERCULIN TEST	TOTAL		LAST TUBERCULIN TEST							
			Positive to 0.01 mg.		Reaction to 1.0 mg.					
	Number	Per cent	Num-ber	Per cent	+++ and ++		+		Negative	
Total.....	339	100.0	81	23.9	40	11.8	37	10.9	181	53.4
Positive to 0.01 mg.	51	100.0	44	86.3	2	3.9	2	3.9	3	5.9
Reaction to 1.0 mg.										
++++, +++ and ++	25	100.0	10	40.0	5	20.0	3	12.0	7	28.0
+	62	99.9	9	14.5	15	24.2	11	17.7	27	43.5
Negative	201	100.0	18	9.0	18	9.0	21	10.4	144	71.6

action was noted; for 5 the intermediate reaction was one-plus to 1.0 mg. before the final negative state was observed. For the remaining 8, the first tests were followed by one, two or three negative readings. With the lessening of reaction and the variability of reaction noted in some of these children, it is evident that the reaction to tuberculin does not always remain constant.

Variables which have not been considered in this paper may be responsible for some of the apparent loss of sensitivity. Nevertheless, it is felt that variables which might influence results, such as composition of population group, technique and testing material, have been the same throughout this investigation. It is believed that the group is sufficiently large for certain conclusions to be made regarding the stability of the reaction to tuberculin. The same staff has carried on the skin testing program in the 5 surveys.

These results of the tuberculin testing program in the school children of Williamson County can be considered in relation to the results of the in-

TABLE 5

Results of serial tuberculin tests of 50 white children and 10 colored children with first tests two-plus or more to 1.0 mg. who were negative on last test

COLOR	SEX	AGE	RESULT OF FIRST TEST	RESULTS OF SUBSEQUENT TESTS			
				2 Year Interval	4 Year Interval	6 Year Interval	8 Year Interval
W	M	15	*++/.01†	†0/1			
W	M	6	+/.01	0/1		0/1	
W	F	6	+/.01		0/1	0/1	
W	F	7	+/.01	+++ /1	+ /1	0/1	
W	F	9	+/.01		0/1	0/1	
W	M	9	+++ / 1		0/1		
W	M	11	+++ / 1	+++ /1	0/1		
W	F	12	+++ / 1	+ /1	0/1		
W	F	12	+++ / 1	0/1			
W	F	14	+++ / 1	0/1			
W	M	5	++ / 1	0/1	0/1	0/1	
W	M	7	++ / 1			0/1	
W	M	7	++ / 1	0/1			
W	M	7	++ / 1	0/1	+ /1	0/1	
W	F	8	++ / 1	0/1			
W	F	8	++ / 1	0/1			
W	F	8	++ / 1		0/1	0/1	
W	M	9	++ / 1		0/1	0/1	
W	F	9	++ / 1	+ /1	0/1		
W	F	10	++ / 1	+++ /1	+ /1	0/1	
W	F	11	++ / 1	+ /1	0/1	0/1	
W	M	11	++ / 1		+ /1	0/1	
W	F	11	++ / 1	+ /1	0/1	0/1	
W	M	11	++ / 1	+ /1	0/1	0/1	
W	F	12	++ / 1	0/1			
W	M	13	++ / 1		0/1	0/1	
W	M	13	++ / 1		0/1		
W	M	14	++ / 1		0/1		
W	F	14	++ / 1	0/1			
W	F	15	++ / 1	0/1			
C	F	6	++ / .01	+ /1	++ /1	+ / .01	0/1
C	M	8	+ / .01	0/1			
C	F	13	+ / .01	0/1			
C	M	7	++ / 1	++ /1	0/1		
C	M	9	++ / 1	0/1			
C	F	9	++ / 1	++ /1	0/1		
C	M	9	++ / 1	0/1			
C	M	11	++ / 1	0/1			
C	F	11	++ / 1	0/1	++ /1	0/1	
C	F	12	++ / 1	0/1			

\* +, ++ and +++ indicate degree of reaction.

† 0 indicates no reaction.

‡ .01 and 1 indicate test dosage of OT in mg.

vestigations by Dahlstrom (9) in Philadelphia. Dahlstrom's material included tests of persons of all ages and of members of families usually followed because of cases of tuberculosis. Of the 2,130 persons found to be positive to the first dose (in Philadelphia), 59, or 2.8 per cent, became negative. In the Williamson County material, of the 144 school children positive to the first dose, 8, or 5.6 per cent, became negative. Considering those with a two-plus or greater reaction to the second dose, nearly half (49.1 per cent) became negative in his series while only one-fourth (24.2 per cent) of those in our series became negative. Also a greater proportion of persons in Dahlstrom's series showing a one-plus reaction to the second dose (70.8 per cent) lost their sensitivity than in our series (45.9 per cent). A longer time period between first and last tests in the Philadelphia study may account for the greater loss of sensitivity.

Edwards and Hardy (19) have studied persistence of sensitivity in children followed in the Tuberculosis Clinic of the Harriet Lane Home of Johns Hopkins Hospital. Children admitted to the clinic were less than two years of age and infected with tuberculosis, as demonstrated by a positive tuberculin test or known to be exposed to sputum-positive tuberculosis. The maximum degree of hypersensitivity demonstrated before the third birthday was used in consideration of persistence of sensitivity. Of the 103 children reacting positively to the 0.01 mg. dose and of the 44 with vesiculated reactions to 0.1 mg., no child sustained a persistent loss of sensitivity. These children were followed for a mean period of seven years. Of the 26 children reacting to 0.1 mg. followed for a mean period of five years, 6, or 23 per cent, lost their sensitivity to this dose and did not regain it; 4 of these, or 15 per cent, were negative to 1.0 mg. dose. Thirty-four children followed for nine years on the average reacted only to 1.0 mg. of tuberculin by the third birthday. The percentage of these losing sensitivity, 19, or 56 per cent, was high and was similar to the percentage of children in Williamson County, giving a one-plus reaction to 1.0 mg. who lost sensitivity. The authors conclude "Those children who developed only a low degree of sensitivity to tuberculin showed a marked tendency to lose their reactivity while those who developed a marked sensitivity, tended to remain hypersensitive."

The results of these investigations indicate that the stability of the tuberculin reaction is related to the degree of reaction. Other factors, in addition to degree of reaction, such as exposure to tubercle bacilli, influence the stability of the reaction. In these investigations, however, only rarely does a person reacting to 0.01 mg. of Old Tuberculin become negative. A high proportion of persons showing only a one-plus reaction to 1.0 mg. lose sensitivity to tuberculin as measured by these two doses of tuberculin.

#### SUMMARY

In Williamson County, during a period when the tuberculosis death rate declined, a reduction in the proportion of school children reacting to tuberculin and a loss of sensitivity in school children given serial tests have been noted. These changes are related to each other and need to be considered in the evaluation of results of tuberculin tests and significance of calcification in the lung fields.

In the 5 school surveys in 1937, 1939, 1941, 1943 and 1945, 5,828 tuberculin tests were completed on white children and 1,478 on colored children. During this period a reduction in the proportion of both white and colored children reacting to tuberculin was noted. The reduction appeared to be less for the older than for the younger children. The tuberculosis death rate has also declined in Williamson County in recent years and thus the opportunities for exposure to tubercle bacilli have been reduced.

The evidence presented in this paper, as well as that from the investigations of others, indicate that sensitivity to tuberculin as measured by two doses of tuberculin frequently disappears over a period of time. The loss of sensitivity is greatest for those who show only a slight reaction on the first test (one plus to 1.0 mg.). For those reacting to 0.01 mg., sensitivity remained during this period of time in 94.4 per cent of the reactors to that test. In the investigation and possible differentiation of tuberculous and nontuberculous calcification utilizing information from skin tests, the fact that sensitivity to tuberculin disappears will have to be considered. The evidence in this paper indicates that, in the general population in Williamson County, loss of sensitivity to 1.0 mg. of Old Tuberculin occurs frequently, and that testing with this dose does not reveal all persons who have been infected with tubercle bacilli.

#### SUMARIO

En el Condado de Williamson, Tennessee, E. U. A., durante un período en que la mortalidad tuberculosa iba en baja, observáronse una disminución en la proporción de escolares positivos a la tuberculina y pérdida de sensibilidad en aquellos en que se hicieron pruebas seriadas. Esos cambios se hallan enlazados y tienen que considerarse al avaluar el resultado de las reacciones a la tuberculina y el significado de la calcificación presente en los campos pulmonares.

En cinco encuestas escolares realizadas en 1937, 1939, 1941, 1943 y 1945, ejecutáronse 5,828 reacciones a la tuberculina en niños blancos y 1,478 en niños de color, notándose en ese período una disminución en la proporción de reactores en ambos grupos, pero menor en los de mayor edad que en los más pequeños. La mortalidad tuberculosa también ha descendido en el Condado de Williamson en los últimos años, lo cual desde luego ha reducido las probabilidades de exposición a los bacilos tuberculosos.

Los datos aportados en este trabajo, así como los derivados de otros estudios, indican que la sensibilidad a la tuberculina, computada con dos dosis de esta sustancia, desaparece frecuentemente al cabo de cierto tiempo. La pérdida de sensibilidad es mayor en los que sólo muestran una reacción leve en la primera prueba (uno más a 1.0 mgm.), en tanto que en 94.4 por ciento de los que reaccionaron a 0.01 mgm., la sensibilidad no se modificó durante ese período de tiempo. En la investigación y posible diferenciación de las calcificaciones tuberculosas y no tuberculosas mediante la información derivada de las cutirreacciones, hay que tomar en cuenta este hecho de la desaparición de la sensibilidad a la tuberculina. Los datos presentados en este trabajo denotan que, en la población general del Condado de Williamson, es frecuente la pérdida de sensi-

bilidad a 1.0 mgm. de Tuberculina Antigua, y que la comprobación con dicha dosis no revela a todos los que han sido infectados por bacilos tuberculosos.

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# CERTAIN EFFECTS OF STREPTOMYCIN ON MYCOBACTERIA IN VITRO<sup>1</sup>

GARDNER MIDDLEBROOK AND DIRAN YEGIAN

Dubos and Davis (1) have described a liquid synthetic medium in which mycobacteria grow more rapidly and more diffusely than in the conventional media. It was of interest to us to investigate the usefulness of this medium for the study of the effects of antibacterial agents on mycobacteria.

## MATERIALS AND METHODS

The microorganisms investigated in these studies were: *M. ranac*, a rapidly growing acid-fast bacillus which is nonpathogenic for mammals; *M. avium*, Kirchberg strain, obtained through the courtesy of Dr. William Feldman; H37Rv, a virulent mammalian strain, kindly supplied by William Steenken, Jr.; and 90 strains of mammalian tubercle bacilli freshly isolated from the sputa of patients with pulmonary tuberculosis. The liquid synthetic medium ("Tween 80" medium) is an aqueous solution of the following composition:

KH <sub>2</sub> PO <sub>4</sub> .....	0.1%
Na <sub>2</sub> PO <sub>4</sub> ·12H <sub>2</sub> O.....	0.625%
Na <sub>2</sub> Citrate.....	0.15%
MgSO <sub>4</sub> ·7H <sub>2</sub> O.....	0.06%
"Casein acids" (Sheffield).....	0.2%
"Vegex" (a yeast autolysate).....	0.05%
"Tween 80" (a water soluble oleic acid ester).....	0.05%
Added aseptically after autoclaving:	
Glucose.....	0.5%
Albumin.....	0.3%

The albumin was heated after neutralization with sodium hydroxide at 56°C. for thirty minutes before being added to the autoclaved medium. The final pH of the medium was 6.8 to 7.0.

The solid medium<sup>2</sup> used for colony counts was prepared by adding to the liquid medium 0.01 per cent ferric ammonium citrate and 2.5 per cent agar (Difco) and by increasing the albumin concentration to 0.5 per cent.

Liquid cultures were grown in 5 ml. amounts in 25 x 150 mm. test tubes. The solid medium was poured into small Petri dishes, 15 ml. per plate, and sealed with "Parafilm" after inoculation with dilutions of liquid cultures in 0.5 per cent albumin and 0.2 per cent agar dissolved in distilled water. All cultures were incubated at 37° to 38°C.

Before any strain was exposed to an antibacterial agent it was cultivated for at least one transfer in the "Tween 80" medium. Constant inocula of 0.1 ml. of

<sup>1</sup> From the New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

<sup>2</sup> Solid modifications of the "Tween 80" medium will be described more fully by R. J. Dubos in subsequent publications.



fully grown cultures (containing approximately 0.2 mg. dry weight of bacilli per ml.) were used for all tests in the liquid medium.

The streptomycin<sup>3</sup> used early in the course of these investigations was not crystalline, but the early experiments have been confirmed and extended with the use of crystalline streptomycin hydrochloride obtained from the same source with the coöperation of Dr. Chester Keefer of the National Research Council. It was dissolved in appropriate dilutions in sterile distilled water and added aseptically to the liquid medium before inoculation. Sulfathiazole and diaminodiphenyl-sulfone, where employed, were added in known concentrations to the culture medium before autoclaving.

#### EXPERIMENTAL

*Susceptibility of three types of mycobacteria to antibacterial effect of streptomycin:* *M. ranae* and H37Rv were initially susceptible (gave no visible growth within fourteen days) to between 0.5 and 1.0 unit (U) of streptomycin (SM) per ml. of medium. *M. avium* Kirchberg was initially susceptible to about ten times this amount of SM. These observations with H37Rv and *M. avium* are consistent with previous reports (2, 3, 4).

*Susceptibility of freshly isolated mammalian tubercle bacilli to streptomycin:* The sputa of 50 unselected hospitalized patients with pulmonary tuberculosis who had never received streptomycin were digested with sodium hydroxide and cultivated on Hohn's glycerine-egg medium. A suspension of one colony of tubercle bacilli was made by trituration in 1 per cent sterile heated albumin in distilled water from a primary culture of each sputum specimen. This was inoculated into the liquid "Tween 80" medium. All of these cultures gave heavy, diffuse growth within two weeks; 0.1 ml. amounts from each "Tween 80" culture were inoculated into 5 ml. amounts of "Tween 80" medium containing varying amounts of streptomycin hydrochloride and to control tubes containing no streptomycin. All control tubes contained heavy growth within fourteen days, whereas all strains were completely inhibited in tubes containing more than 1 U SM per ml. and partially inhibited in 0.5 U SM per ml.

To determine whether or not previous cultivation in Hohn's medium affected the sensitivity of tubercle bacilli from human beings, 40 more sputa were cultivated directly in "Tween 80" medium after sodium hydroxide digestion. These were tested on second transfer as were the suspensions from Hohn's medium and the results were entirely similar to those obtained by the first technique. Thus, mammalian strain tubercle bacilli from 90 patients with pulmonary tuberculosis were uniformly susceptible to between 0.5 and 1.0 U SM per ml. in "Tween 80" medium.

*Nature of antibacterial action of streptomycin on mycobacteria:* Unconvincing evidence has been presented to indicate that streptomycin is "bactericidal" for tubercle bacilli (5). It seemed to us that the use of "Tween 80" liquid medium and of its solid modification would provide more accurate information concerning the ability of tubercle bacilli to multiply after exposure to streptomycin. Two

<sup>3</sup> Supplied through the courtesy of Dr. D. F. Robertson of Merck & Company.

approaches to this problem were used. The first was to determine whether resting cells would multiply when transferred in high dilution from a solution to which streptomycin was added to agar plate medium free of streptomycin, and the second was to perform the same experiment with multiplying cells in the "Tween 80" medium.

A resting cell suspension was prepared by centrifuging a culture of H37Rv which had just attained grossly visible growth, washing it once in 0.85 per cent saline and then resuspending it in 0.85 per cent saline. After twenty-four hours in the incubator, 0.1 ml. of this suspension was diluted in semisolid agar-albumin to  $10^{-4}$ ,  $10^{-5}$ ,  $10^{-6}$ ,  $10^{-7}$  dilutions and 0.5 ml. of each dilution was pipetted onto the surface of "Tween 80" solid medium. Immediately thereafter 0.5 ml. of sterile distilled water containing sufficient streptomycin to give a final concentration of 20 U SM per ml. was added to the suspension of resting cells. The plating procedure was repeated in twenty-four and again in seventy-two hours. The plates were examined after eighteen days' incubation. The results indicated that exposure of resting tubercle bacilli to SM did not affect to any appreciable extent their ability to multiply even after seventy-two hours' exposure.

The same procedure was carried out with multiplying cells of the same strain by adding the same amount of SM to a culture of H37Rv in "Tween 80" medium which had just attained grossly visible growth. Examination of the plates at the end of eighteen days' incubation revealed that no tubercle bacilli multiplied after seventy-two hours exposure to 20 U SM per ml. and that more than ninety-nine per cent of the cells failed to multiply after exposure for twenty-four hours to the same concentration of SM. Whether or not this result indicates a true (irreversible) bactericidal effect of streptomycin upon multiplying tubercle bacilli remains to be seen.

*Development of strains of mycobacteria resistant to streptomycin:* Three cultures of mycobacteria were rendered resistant to the antibacterial effects of SM. The technique of producing a resistant strain was as follows. The parent susceptible culture was inoculated into "Tween 80" medium containing 0.25, 0.5, 1, 2, 4, 8 etc. U SM per ml. and incubated until there was maximum growth in the control tubes containing no SM, at which time subcultures were made from that tube which showed approximately 50 per cent of the growth of the control tube. This procedure was repeated for each of the three types of mycobacteria. *M. ranae*, *M. avium* Kirchberg and H37Rv, until a strain of each was obtained which grew well in 1000 U SM per ml. The times which this took was proportional to the rates of growth of the three types of mycobacteria in this medium: four weeks for *M. ranae*; six weeks for *M. avium*; and fourteen weeks for H37Rv. If larger inocula than 0.01 ml. were used, the rate of development of resistance was increased. Thus mycobacteria, like other microorganisms (6), develop resistance to SM at a rapid rate *in vitro*. A recent preliminary clinical report (7) indicates that this also occurs *in vivo*.

*Specificity of resistance:* *M. ranae*, previously rendered resistant to 200 mg. per cent sulfathiazole (8), was tested for streptomycin susceptibility and found to be just as susceptible as the original sulfathiazole-susceptible strain. It was

then rendered resistant to 200 U SM per ml. by the same technique and in the same length of time as was necessary in the case of the original sulfathiazole-susceptible strain; its resistance to sulfathiazole remained unchanged. An original culture of *M. ranae* was made resistant to SM and then tested for susceptibility to sulfathiazole; it was just as susceptible to sulfathiazole as was the original SM-susceptible culture. Entirely similar observations have been made with H37Rv. Thus susceptibilities of mycobacteria to streptomycin and to sulfathiazole are specific and independent states.

*Effect of sulfonamide upon development of resistance to streptomycin:* Attempts have been made to develop strains of *M. ranae*, *M. avium* and H37Rv resistant to both streptomycin and sulfathiazole by cultivating them in serial transfer in increasing concentrations of both these agents simultaneously. These efforts have been relatively unsuccessful, although after many transfers over a period of four months in very gradually increasing concentrations of both agents it has been possible to obtain a strain of *M. ranae* which will grow in 5 mg. per cent sulfathiazole and 50 U SM per ml. A similar result has been encountered in an attempt to develop a strain of H37Rv resistant to SM and diaminodiphenyl-sulfone simultaneously.

Quantitative investigation of the nature of the development of strains of staphylococci resistant to penicillin indicate that resistance originates as a change comparable to the selection of spontaneously occurring variants (9, 10). It seems likely that a similar phenomenon is taking place in the acquisition of resistance of mycobacteria to streptomycin and sulfonamides. Thus our observations on the retardation of the development of resistance of mycobacteria by cultivation in the presence of two different types of antibacterial agents simultaneously can be explained by assuming that the chance of the appearance of a variant resistant to both agents is equivalent to the product of the chances of the appearances of variants to each agent separately: The implications of the fact are of obvious clinical significance wherever prolonged chemotherapy is essential. The explanation could also apply to other reported examples of apparent additive or synergistic effects of antibacterial agents *in vitro* and *in vivo* (11, 12, 13, 14, 15), although theoretically other mechanisms may underlie the phenomenon of marked antibacterial synergism.

*Permanence of resistance:* We have observed that the development of resistance of *M. ranae* to sulfonamides was a permanent variation (8). It was therefore of interest to determine whether or not acquisition of resistance to streptomycin was also a permanent change in mycobacteria. The three strains of mycobacteria which had acquired high resistance to SM were transferred many times on glycerine-egg medium and in "Tween 80" medium and have been shown to maintain their degrees of resistance unchanged over a period of four months, at least.

*Resistance and virulence:* The highly resistant strain of H37Rv was tested for virulence by injecting 0.01 mg. dry weight of living organisms from "Tween 80" liquid medium into the groins of each of 4 guinea pigs. Four other guinea pigs were similarly injected with the same weight of living streptomycin-susceptible H37Rv grown in the same medium. The course of the infection was the same in

the two groups: generalized tuberculosis was present in all animals within six weeks.

#### SUMMARY AND CONCLUSIONS

1. Freshly isolated tubercle bacilli from patients with pulmonary tuberculosis appear to have a uniform susceptibility to streptomycin *in vitro*.

2. Exposure of tubercle bacilli to streptomycin in relatively low concentration *in vitro* inhibits subsequent multiplication of multiplying but not of non-multiplying tubercle bacilli when they are transferred to medium free of streptomycin.

3. All mycobacteria thus far tested develop resistance to streptomycin *in vitro* at a rapid rate.

4. Resistance to streptomycin persists for at least four months and appears not to be paralleled by any diminution in virulence for guinea pigs.

5. The acquisition of resistance of mycobacteria to streptomycin is independent of their acquisition of resistance to a sulfonamide (or a sulfonamide-like agent) and the development of resistance to these drugs is retarded when mycobacteria are exposed to both types of agents simultaneously. The probable explanation of this phenomenon is discussed.

6. The use of "Tween 80" medium has greatly facilitated the study of the effects of antibacterial agents upon mycobacteria.

#### SUMARIO Y CONCLUSIONES

1. Los bacilos tuberculosos recién aislados de enfermos de tuberculosis pulmonar parecen mostrar una susceptibilidad uniforme a la estreptomicina *in vitro*.

2. La exposición de los bacilos tuberculosos a concentraciones relativamente bajas de estreptomicina *in vitro* inhibe la multiplicación subsiguiente de los bacilos que se multiplican, pero no de los que no se multiplican, al ser trasladados a un medio sin estreptomicina.

3. Todas las micobacterias comprobadas hasta la fecha desarrollan rápidamente resistencia a la estreptomicina *in vitro*.

4. La resistencia a la estreptomicina dura por lo menos cuatro meses y aparentemente no va acompañada de la menor disminución de la virulencia de los bacilos para los cobayos.

5. La adquisición por las micobacterias de resistencia a la estreptomicina es independiente de su adquisición de resistencia a un sulfonamido (o sustancia sulfonamidoidea), y la aparición de resistencia a estas últimas drogas se retarda al exponer simultáneamente a las bacterias a ambas clases de sustancias. Discútese la probable explicación de este fenómeno.

6. El empleo del medio "Tween 80" ha facilitado considerablemente el estudio de los efectos de los agentes antibacterianos sobre las bacterias.

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# SYNTHESIS OF B-COMPLEX VITAMINS BY TUBERCLE BACILLI WHEN GROWN ON SYNTHETIC MEDIA<sup>1,2</sup>

HILDA POPE AND DAVID T. SMITH

Tubercle bacilli, of both human and bovine variety, grow readily on synthetic media which are completely devoid of preformed vitamins, although the B-complex vitamins have been found essential for the growth of all bacterial cells studied up to the present time.

In 1938 Boissevain and coworkers (1) isolated and measured the riboflavin content of Sauton's medium upon which 4 different strains of tubercle bacilli had grown. Landy and Dicken (2) have reported the synthesis of biotin by tubercle bacilli and Landy, Larkum and Ostwald (3) the synthesis of p-aminobenzoic acid.

The objectives of this investigation were (1) to confirm the results of the authors mentioned above, (2) to extend the study to 6 other members of the B-complex and (3) to determine whether quantitative differences occur in the comparative synthetic abilities of human and bovine strains which might lead to a possible explanation of variation in their rate of growth on synthetic media.

## EXPERIMENTAL

Two virulent strains of the tubercle bacillus were studied: the human organism, H37, and the bovine strain, Ravel. Initial cultures were obtained from the Saranac Lake Laboratory and grown on Vorwald's modification of Proskauer-Beck's synthetic medium.

One hundred cc. aliquots of the medium were seeded with one loopful of organisms from a six-weeks old culture and incubated at 37°C. The age of the cultures used for inoculation and the size of the inoculum were always the same. Following a six weeks' growth period the organisms were separated from the filtrate and sterilization accomplished by use of a Seitz filter.

A comparison of dry cell weights and macroscopic observations of the comparative amount of growth of the two strains, as determined by noting the appearance of the pellicle and the amount of surface covered, showed that cell proliferation by the human strain was approximately three times that of the bovine organism.

The cell-free filtrate was adjusted to the proper pH and used without further treatment in testing for the presence of the 9 B-complex vitamins. Standard microbiological assay procedures (4 to 11) were used in making all of the analyses, except in the case of riboflavin where a fluorometric method (12) served as a check on the microbiological procedure. Vitamins tested for include biotin, folic acid, inositol, nicotinic acid, p-aminobenzoic acid, pantothenic acid, pyridoxine, riboflavin and thiamin.

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<sup>2</sup> This study was financed in part by a grant from the John and Mary R. Markle Foundation.

The basic medium was titrated repeatedly for the presence of vitamins before it was inoculated with the bacilli and these titrations were always negative.

Table 1 gives the results obtained from quantitative vitamin determinations on human and bovine filtrates.

TABLE 1  
*Vitamin synthesis per milliliter of tubercle bacillus medium filtrate*

VITAMIN	STRAIN OF ORGANISM	
	H37	Ravanel
Biotin.....	0.002 $\gamma$	0.001 $\gamma$
Folic acid.....	0.015 $\gamma$	0.002 $\gamma$
p-Aminobenzoic acid.....	0.020 $\gamma$	0.002 $\gamma$
Thiamin.....	0.041 $\gamma$	0.014 $\gamma$
Riboflavin.....	0.330 $\gamma$	0.060 $\gamma$
Pantothenic acid.....	0.410 $\gamma$	0.140 $\gamma$
Pyridoxine.....	0.440 $\gamma$	0.090 $\gamma$
Inositol.....	14.170 $\gamma$	1.280 $\gamma$
Nicotinic acid.....	37.500 $\gamma$	0.740 $\gamma$

#### DISCUSSION

The results obtained in this investigation would lead one to believe that tubercle bacilli actually require accessory nutritive factors. Preformed vitamins are not required as such since the organism possesses the ability of building up these complex organic compounds from substances incorporated in the culture medium. In the case of each of the 9 vitamins studied, after a six weeks' growth period an appreciable amount of each member of the group had been synthesized to render it easily measurable by sensitive microbiological techniques.

A comparison of the data of human and of bovine organisms reveals significant differences. With each vitamin under consideration, synthesis by the human type organism was greater than by the bovine. Since the culture medium used is not equally satisfactory for the growth of both strains, this factor must be accounted for. The three-fold difference between growth of the two strains, however, is insufficient to account entirely for variations in their synthetic abilities.

Chart 1 shows graphically variations in synthetic ability between the human and bovine strains taking this growth difference into consideration. Vitamins synthesized are plotted as ratios. In each case synthesis by the Ravanel organism is taken as 1 and values given for the H37 strain represent ratios of H37 to Ravanel synthesis of each vitamin. The H37 expectancy line shows the general trend that would normally be anticipated if only a difference in amount of growth were involved in differences of synthetic abilities of the two strains. A deviation of 2 units on either side of the expectancy line is allowed to account for errors introduced as a result of deficiencies in methods of analysis.

The most striking variation observed is the difference in nicotinic acid synthesis. Nicotinic acid production by the human strain is approximately fifty times

as great as that of the bovine organism. The human strain synthesized 37.5  $\gamma$ , while only 0.74  $\gamma$  of nicotinic acid was elaborated by the bovine type bacillus.

Other deviations, while less striking than that of nicotinic acid, are also suggestive of underlying variations in actual synthetic abilities of the two strains. Such deviations are observed with folic acid, inositol and p-aminobenzoic acid, where the human bacillus produces seven, eleven and ten times as much of the given vitamin, respectively, as the bovine organism.

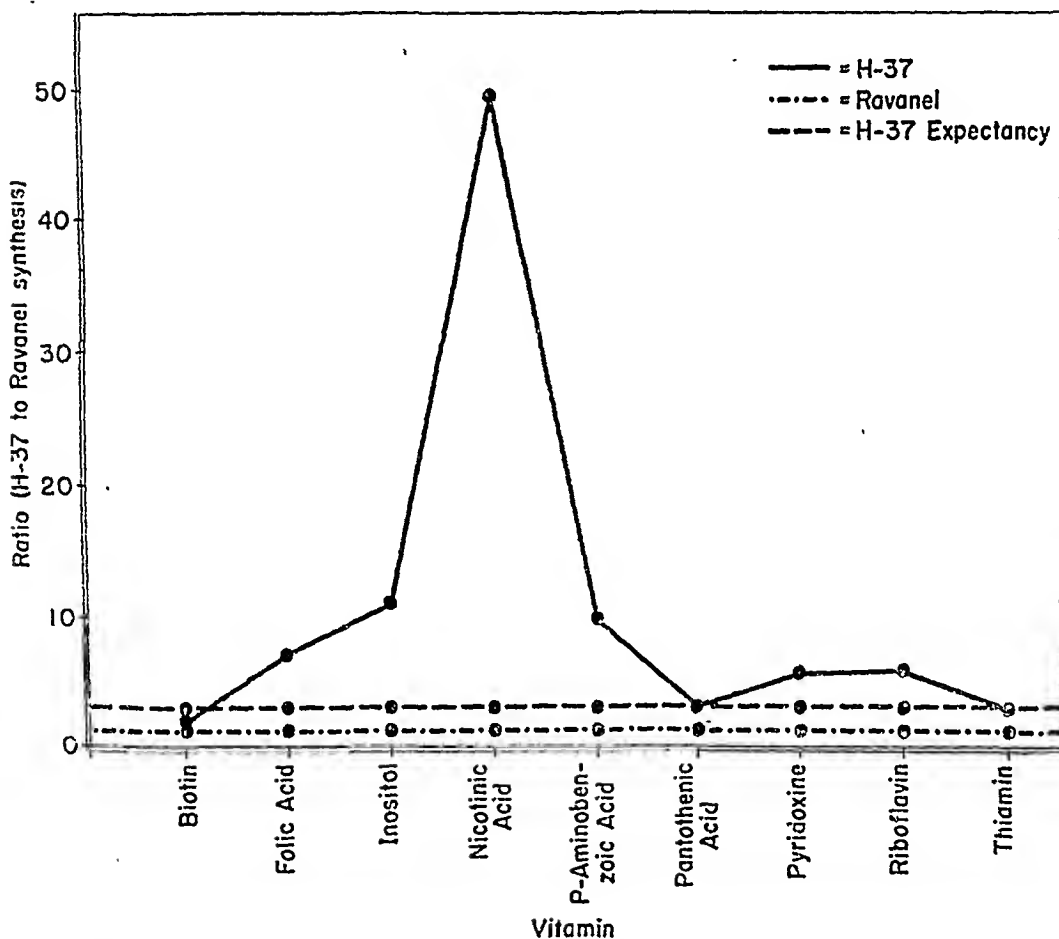


CHART 1. Variations in vitamin synthesis by H37 and Ravel strains of the tubercle bacillus.

These variations in vitamin synthesis by the two strains of organisms studied would seem to indicate that we are dealing here with fundamental differences between the human and bovine bacillus, equally as important as other long-established cultural variations. Whether these differences in synthetic ability in regard to the B-complex vitamins account for the prolonged lag in the early growth period of the bovine organism, or whether the actual requirements of the two strains vary, it is impossible at this point to say. Therefore, we can only



offer the suggestion that such an explanation of the lag period on the basis of varied synthetic abilities is a possibility quite logical in view of our present findings.

#### SUMMARY

1. A study of the synthesis of vitamins of the B-complex by the tubercle bacillus was undertaken (1) to confirm previous reports of synthesis of riboflavin, biotin and p-aminobenzoic acid, (2) to extend the study to other members of the B-complex and (3) to discover if significant differences exist in the synthetic powers of human and bovine strains of the organism.

2. H37 and Ravel strains of the tubercle bacillus were cultured on a synthetic medium, and the cell-free filtrate analyzed for the presence of the B-complex vitamins.

3. The following 9 vitamins were found to have been synthesized by both strains of the tubercle bacillus: biotin, folic acid, inositol, nicotinic acid, p-aminobenzoic acid, pantothenic acid, pyridoxine, riboflavin and thiamin.

4. Appreciable differences were observed in the amount of nicotinic acid, p-aminobenzoic acid, folic acid and inositol synthesized by human and bovine strains. These differences were too marked to be credited entirely to the greater cell proliferation of the human type organism.

#### SUMARIO

1. Empezóse este estudio de la síntesis de las vitaminas del complejo B por el bacilo tuberculoso, a fin de: (1) confirmar previas comunicaciones sobre la síntesis de la riboflavina, la biotina y el ácido p-aminobenzoico, (2) para extender el estudio a otros miembros del complejo B, y (3) para descubrir si existen diferencias significativas en las facultades sintéticas de las cepas humana y bovina del microbio.

2. Las cepas H37 y Ravenel del bacilo tuberculoso fueron cultivadas en un medio sintético, analizándose después el filtrado exento de células, en cuanto a la presencia de vitaminas del complejo B.

3. Descubrióse que las siguientes nueve vitaminas habían sido sintetizadas por ambas cepas del bacilo tuberculoso: biotina, ácido fólico, inositol, ácido nicotínico, ácido p-aminobenzoico, ácido pantoténico, piridoxina, riboflavina y tiamina.

4. Observáronse diferencias apreciables en la cantidad de ácido nicotínico, ácido p-aminobenzoico, ácido fólico e inositol sintetizada por las cepas humana y bovina, siendo las diferencias demasiado grandes para poderlas atribuir por completo a la mayor proliferación celular del microbio de tipo humano.

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# THE RELATIONSHIP OF ACQUIRED RESISTANCE, ALLERGY, ANTIBODIES AND TISSUE REACTIVITIES TO THE COMPONENTS OF THE TUBERCLE BACILLUS<sup>1,2,3</sup>

SIDNEY RAFFEL

About three years ago we undertook the study of acquired resistance and other immunological responses associated with tuberculosis, from the viewpoint of an analysis of the host's activities in relation to the isolated components of the bacillus.

The knowledge that already exists of such relationships is highly stimulating. At least two of the major alterations induced in the body may be accounted for on the basis of isolated and purified bacillary constituents. The cellular elements which compose the proliferative tubercle may appear as the result of the injection of the phosphatide of *M. tuberculosis* into normal tissues; the wax of the organism has a similar property (1). Such "anatomical tubercles" are entirely lacking in the element of infectiousness, but in both instances the quantities of these lipids necessary to effect such tissue responses are disproportionately large as compared with the effectiveness of small numbers of bacilli in this regard. Again, the hypersensitivity of tuberculous infection is clearly a response to the protein within the bacillus (2), but there has been no convincing evidence that this reactive status can be induced by treatment of normal animals with the protein itself. Only whole bacilli, living or dead, have been found successfully to initiate the "tuberculin type" of hypersensitiveness (3, 4).

Acquired resistance, although it is concrete enough in demonstration, has remained so far unexplained in nature. Lurie (5) has provided ingenious evidence that both fluids and cells of the immune animal contribute to the resistant state. The mechanisms by which either contribute, and in response to what kind of impetus supplied by the bacillus, are questions for which clear answers have not been supplied.

Our earlier efforts to expand such information were centered on the possible rôle of the polysaccharide of the tubercle bacillus in providing the stimulus for acquired immunity. The reasons for this have been set forth before (6). It was hoped that evidence for such a rôle of bacillary polysaccharide would not only relate immunity to the responsible portion of the organism, but would also set on the firm basis of immunological specificity the relationship, or lack of relationship, of this response to allergy.

As our work progressed it became apparent that the study could not remain restricted to this single response and this single bacillary substance. The results

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<sup>2</sup> The work on which this report is based has been supported since 1943 by the California Tuberculosis and Health Association and the National Tuberculosis Association.

<sup>3</sup> Presented before the Medical Section at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 12, 1946.

which are reported, therefore, include integrated observations concerning several bacterial constituents and four concomitant types of host responses.

On the side of the bacillus we have studied the effects of the following materials: carbohydrates, unheated protein, phosphatide (crude and purified) and acid-fast wax.<sup>4</sup> In addition, we have employed bacilli deprived of phosphatide and wax by ether-alcohol and chloroform extraction, defatted bacilli to which lipids were re-added, bacilli killed by moderate heat and living BCG organisms. The various isolated bacillary preparations may be described briefly as follows:

The carbohydrate has, in the main, been that which is readily extractable by aqueous vehicles from the synthetic culture medium on which bacilli have grown, or from defatted bacillary bodies. Limited experiments have also been carried out with polysaccharides split off from the phosphatide, the wax and the firmly bound lipids of the bacillus.

Unheated protein is obtained from synthetic culture fluid or from defatted bacillary bodies by extraction with phosphate buffer at pH 7.3. The protein is reprecipitated eight times in the cold by half saturation with ammonium sulphate at pH 7.0. This is antigenic protein in as close an approximation to the native state as ordinary chemical methods permit.

Two phosphatide preparations have been employed. Our own material was obtained by extracting unkilld virulent bacilli with an equal mixture of ether and ethyl alcohol, through which carbon dioxide had been bubbled. The total extraction period was five weeks. The extract was filtered through Seitz pads under carbon dioxide pressure, then brought to dryness in a stream of carbon dioxide. This is the "crude phosphatide" of Anderson (7). It was deliberately employed without further purification so that any biological effect of "impurities" (from the organic chemical viewpoint) would be detected. A sample of purified phosphatide for comparative work was kindly supplied by Dr. R. J. Anderson. No difference in activity of the two preparations was noted in our experiments.

The chloroform soluble waxes were obtained from bacilli previously extracted with ether-alcohol and subjected for a five week period to carbon dioxide treated chloroform. This extract was filtered through Seitz pads under carbon dioxide pressure and evaporated to dryness under a stream of carbon dioxide. The yellow brittle wax was then dissolved in a small volume of toluene (of specific gravity of 0.86) and centrifuged for two hours to eliminate any bacterial bodies which might still be present. The toluene solution was then redried under a stream of carbon dioxide.

With such materials, some representing several sources and methods of preparation, we have injected guinea pigs over long periods (three to six months) and have sought correlated information on these points: the ability of animals so treated to resist subsequent infection, the development of the tuberculin-type of allergy, the responses of tissues to other bacillary components as manifested by skin reactivity, and the production of antibodies to various chemical components of the bacillus.

The current results of these trials are expressed in condensed and rather un-

<sup>4</sup> Samples of carbohydrate as well as phosphatide, for comparison with our own and for confirmation of results, have been kindly supplied by Dr. R. J. Anderson of Yale University. Volumes of synthetic medium culture to supplement our own for isolation of bacillary constituents, and large quantities of Old Tuberculin, have been generously provided by the Cutter Laboratories of Berkeley, California.

qualified form in table 1. These data represent observations made at the completion of the series of injections of each of the types of vaccines listed, and

TABLE 1  
*Integration of immunological responses in guinea pigs*

PREPARATIONS INJECTED	NUMBER OF ANIMALS	NUMBER OF INJECTIONS	MG. EACH IN- JECTION	TOTAL PERIOD OF INJECTIONS IN WEEKS	RESISTANCE AND ALLERGY*		SKIN RESPONSES†				ANTIBODY RESPONSES (COMP. FIX.)					
					Re- sist- ance	Al- lergy	OT	H.M.W. Pro- tein	Polysac- charide‡	Phos- phatide	OT	H.M.W. Protein	Polysac- charide‡	Phos- phatide	Wax	Whole Bacil- lary Antigens
BCG.....	46	5	5	13-28	+	+	+	+	+	-	+	+	-	+	+	+
Heat-killed bacilli.....	16	10	10	13	-	+	+	+	+	-	+	+	±**	+	+	+
Defatted bacilli (phosphatide and wax ex- tracted).....	24	10	10	13	-	-	-††	No test	-††	-	-	+	-	-	-††	+
Defatted bacilli + phosphatide....	22	10	10 + 5	13	-	-	-††	No test	-††	-	-	+	-	-	-†	+
Defatted bacilli + wax.....	9	10	10 + 5	13	-	+	+	+	+	-	±	+	-	-	-†	+
Phosphatide.....	18	10	5	13	-	-	-	-	-††	-	-	-	-	-	-	-
Wax.....	29	10	5	13	-	+	+	+	+	-	-	+	-	-	-†	+
H.M.W. protein†.	9	10	5	13	-	-	-	+‡	-	-	-	+	-	-	-	-
H.M.W. protein† + phosphatide..	8	10	5 + 5	13	-	-	-	+‡	-	-	-	+	-	-	-	±
Polysaccharide§..	18	10	0.01 to 1.0	13	-	-	-	-	-	-	-	-	-	-	-	-

\* Tuberculin-type allergy determined by skin reactivity to Old Tuberculin and reaction to subcutaneous injection of living virulent bacilli.

† The range of doses employed to elicit these responses were as follows:

OT—0.1 cc. 1:10 through 1:500.

H.M.W. protein—0.5 mg. through 0.01, doses comparable to those of OT on basis of protein content.

Polysaccharide—0.1 mg.

Phosphatide—0.1 mg.

‡ H.M.W. protein is the "high molecular weight" antigenic protein described in the text.

§ Polysaccharide extractable by aqueous solutions from medium or defatted bacillary cells, as described in text.

\*\* One animal has been found to produce demonstrable antibody of this kind.

†† Reactions in occasional animals.

‡‡ These responses to high molecular weight protein were of the urticarial type, fading after twenty-four hours.

Note: In this table the symbols represent the trend of reactions in the majority of animals of the groups listed.

immediately preceding the inoculation of virulent bacilli as a test for resistance. Although similar determinations were made periodically during the immunization

period and throughout the course of infection, it is just preceding test infection that an animal should reveal those acquired qualities which will serve to protect it. The profusion of symbols may be reduced to a few simple conclusions.

1. *Acquired resistance*: We have been unable to demonstrate the appearance of acquired resistance in animals treated with any preparation except BCG. In view of reports (8, 9) of the successful immunization of animals and possibly of man with heat-killed bacilli, we have repeated these trials several times, with two different strains of moderately virulent human tubercle bacilli. Whatever slight benefits may have resulted to guinea pigs so prepared, they have appeared to us highly equivocal when contrasted with the resistance revealed by the simultaneously observed BCG immunized animals. It is important to note in this connection that our criteria of resistance, our infecting doses and the host of choice for these studies have all combined to constitute a crucial test for resistance. The criteria of resistance are based on observations of regional lymph node involvement following subcutaneous infection, weight fluctuation, survival time and gross and microscopic pathological examinations. Of these, the last has proved most reliable, and an effort has been made to take account only of significant differences between variously treated groups of animals. Our challenge doses of virulent bacilli have been large (1 mg. wet weight of H37 or H37 Rv), because earlier experiences taught us that with smaller numbers of bacilli which may approach the spontaneous infection range, the element of infection-resistance complicated our interpretations to the point of uselessness. So far as the host is concerned, the meagre native resistance of the guinea pig to *M. tuberculosis* is too well known for comment; this is of especial interest because some of the more extensive work which has resulted in a judgment of efficacy of heat-killed bacilli as immunizing agents has been carried out in the relatively (natively) resistant rabbit (9).

A detailed discussion of the rôle of the host in the evaluation of vaccines is actually beside the point for our purposes. We are seeking to relate unequivocal resistance in the guinea pig to the stimulating factor in the bacillus and for this purpose a stringent set of requirements seems more rational than one which is too susceptible to subjective interpretation.

As is evident from the table, no one of the bacillary components so far tried, alone or conjointly, has resulted in resistance to tuberculosis.

2. *Allergy*: The classical hypersensitivity to the protein of the tubercle bacillus has been considered in the table together with resistance, because of the controversial aspects of their possible relationship. As has been indicated, acquired resistance has been observed only in BCG immunized animals, in which there is a simultaneous occurrence of allergy. On the other hand, in addition to heat-killed bacilli, it has been possible with two of the antigen preparations used to reproduce the delayed type of tuberculin allergy in the complete absence of resistance. Examination of the table reveals that the important element which enters into "artificial" sensitization of the tuberculin type is the bacillary wax, and the order of listing provides an evolutionary outline of this observation. We first found in several repeated experiments that groups of animals repeatedly

injected with large doses (10 mg.) of bacilli which had been subjected to extraction for removal of phosphatides and waxes did not develop significant hypersensitivity to Old Tuberculin. On re-adding each of these lipids to such bacilli, it was found that the waxes restored the sensitizing power. When now the isolated protein was combined with wax, sensitization occurred and, furthermore, the wax by itself produced the same effect. This has been noted with two separate wax preparations in different experiments. We have gone to considerable pains to free the wax of residual bacilli (even though any present would be of the non-sensitizing defatted type in any case) by Seitz filtration and subsequently by dissolving the material in a solvent (toluene) of low specific gravity and centrifuging for a prolonged period. Tubercle bacilli have not been found in the sediments of such preparations.

It is obvious then that protein in antigenic form persists in the chloroform extracts which contain the wax, despite the well known protein denaturant action of this organic solvent. The presence of protein is indicated not only by the fact of sensitization to tuberculin, but in addition by the demonstration in the serum of all guinea pigs receiving the waxes of the presence of antibody for protein. In addition, these animals at infection demonstrated a modified Koch reaction to inoculation of bacilli; i.e., there was induration and erythema but no necrosis.

The quantitative aspects of the wax-induced hypersensitivity and the criteria by which this is distinguished from anaphylactic sensitivity have not been completely investigated as yet. Some information on these points is available, however, as detailed below.

With regard to quantitation, the earliest skin tests with Old Tuberculin have been performed following the second injection of 5 mg. of wax, eighteen days after the beginning of treatment. At this time all of 20 animals reacted to OT 1:10, and several days later a titration of responsiveness revealed that about half the guinea pigs reacted to OT up to a dilution of 1:500. This approaches the range or reactivity of the guinea pig during the course of tuberculous infection. Whether tuberculin reactivity may occur earlier and whether after further injections of wax the level of hypersensitivity increases, are points currently under study.

The criteria which establish that hypersensitivity is of the delayed tuberculin rather than the anaphylactic type are multiple, and must be fully satisfied before the claim can be justified that tuberculin allergy has been produced without the presence of whole bacilli in the tissues. The hypersensitivity of tuberculosis and of some other infectious diseases differs from anaphylactic hypersensitivity in several basic respects. A major item is the fact that allergy of the tuberculin type involves all tissues of the body, whereas hypersensitivity of the anaphylactic type makes itself evident in contraction of smooth muscle and alterations in vascular endothelium. This characteristic of tuberculosis hypersensitivity, the vulnerability of all cells to contact with antigen, is closely related to the pathogenesis of the disease, for in the highly sensitive body it leads to cellular necrosis.

At this time we have at hand evidence of several kinds to indicate that we are

dealing with delayed tuberculin-type hypersensitivity in guinea pigs treated with wax-protein.

(a) Animals treated with the protein-containing wax preparation subsequently react to Old Tuberculin injected intracutaneously. As opposed to this, it has been common experience that animals in which anaphylactic hypersensitivity has been induced with tuberculo-protein alone develop skin reactivity to homologous protein only and not to Old Tuberculin.

(b) The character of the skin reaction to Old Tuberculin appears to be typical of that seen in infected animals.

(c) In 4 animals injected parenterally with 2.0 cc. of Old Tuberculin, no symptoms or signs of anaphylaxis were seen. All animals became ill—weak and restless—during the subsequent eight hours, and one died at seventy-two hours. Normal animals which received such injections at the same time were entirely unaffected.

(d) Two animals which received 16 mg. of high-molecular-weight protein intravenously showed no indication of the anaphylactic syndrome. Subsequently there was weakness persisting for eight hours, but no deaths.

(e) A group of 9 wax treated animals received 1.0 mg. wet weight of living bacilli subcutaneously as an infecting dose. All developed erythema and induration at the site, demonstrable at twenty-four and forty-eight hours. This compared in degree with similar reactions observed in groups of animals receiving the same infective dose at the same time after prolonged immunization with BCG, and with heat-killed bacilli. On the other hand, groups of animals which had been vaccinated with defatted bacilli, with defatted bacilli mixed with phosphatide, with unheated protein or with this protein mixed with phosphatide, and a group of untreated control guinea pigs, showed no indication of altered reactivity to the infecting dose of bacilli. This direct comparison was especially convincing in indicating that the wax treated group of pigs, with regard to hypersensitivity, behaved like groups of animals which had been sensitized by means of injections of whole tubercle bacilli.

(f) The uterine horns were removed from 4 wax treated animals and tested *in vitro* by the Schultz-Dale method for reactivity to Old Tuberculin. None of the 8 horns revealed any reactivity whatever to this substance, although the viability of the smooth muscle was proved in each instance by the occurrence of marked contraction on the addition of histamine to the bath.

(g) The sera of 3 wax treated animals were injected into normal guinea pigs. Each serum was administered intraperitoneally into one normal animal and intracutaneously into a second. Twenty-four hours later the 6 animals were tested for skin reactivity to Old Tuberculin; the guinea pigs which had received serum intracutaneously were injected into the same sites with tuberculin. There was no indication in any instance that this sensitivity was passively transferable by serum.

A final criterion involves the explantation of tissues of hypersensitive animals into culture and the demonstration of cellular death on contact with tuberculin.



This is presently under investigation; at the same time we are engaged in extending the other lines of evidence described above.

In summary then, all the evidence which we have so far had the opportunity to accumulate points in the same direction; namely, that the hypersensitivity established in guinea pigs by protein-wax of the tubercle bacillus is of the delayed tuberculin-type.

Since the allergic state thus appears to be induced by isolated components of the bacillus, and since animals so sensitized have shown no indication of resistance to tuberculous infection, it appears that the antigenic component which evokes hypersensitivity is not the stimulus responsible for setting up the resistant state. To complete this segregation of host reactions to bacillary components, it is highly desirable that we should be able to produce with the proper isolated substance a positive reaction limited to the first column of the table—resistance unencumbered by allergy. This has so far been unsuccessful, but in view of the chemo-immunological evidence already at hand it is difficult to subscribe to the view that the allergic state, that is, reactivity to the protein of the tubercle bacillus, constitutes a significant part of the resistance to tuberculosis.

3. *Tissue reactions:* The responses of the tissues of immunized guinea pigs to fractions of the bacillus other than the protein have also been studied. It has been our endeavor to reveal the relationship of acquired immunity to a particular component of the bacillus by such a method, or by demonstrating a particular humoral antibody present only in the resistant animal, as discussed in the following section. Only a limited number of different fractions have been employed, but these have undergone concentrated study, varying the methods of preparation, purity of fractions, doses and so forth.

It is evident that as regards protein, two groups of animals immunized with this material, alone or mixed with phosphatide, did not develop reactivity to Old Tuberculin. These did however become hypersensitive to "high-molecular-weight" protein, the unheated antigenic material obtainable from synthetic culture medium or bacillary bodies. But such hypersensitivity is well delineated from that which we know as tuberculin-type allergy; this difference has been clearly defined by Rich (3). Those animals in which protein reactivity was limited to the high-molecular-weight material showed skin reactions which disappeared after twenty-four hours and were of the Arthus type rather than of the tuberculin-type.

Grossly demonstrable tissue reactivity to carbohydrate does not occur in the skin of normal guinea pigs when small doses (0.1 mg.) are employed for injection. Skin reactions have been observed in the groups of treated animals indicated in the table, however, under conditions wherein contamination of the preparations with protein has been excluded as the causative factor. This has been so consistent an observation that we feel little doubt of its independent existence (10, 11). This reactivity is manifested also as an anaphylactic type of response, the dermal edema and erythema reaching a peak at from eight to twenty-four hours and usually fading entirely by forty-eight hours. We have tried to determine the correlation of this response with resistance but, although it is more intense in

resistant groups (BCG), it occurs also in other series of animals without acquired resistance, and we are not prepared at this time to assess this tissue activity with respect to acquired immunity.

4. *Antibodies*: A good deal of our effort has been devoted to the analysis of antibody responses of animals following their courses of injections and immediately prior to challenge infection. There are extant many reports concerning the immune bodies as related to acquired resistance, but our interest was specifically directed toward the individual antibodies to individual components of the cell. It is entirely possible, when testing for antibody by the use of whole bacillary antigen, to find that positive reactions occur with the sera of animals which may or may not be resistant. But the important issue is not whether antibodies reacting with the whole cell have been produced, but whether there is antibody to the particular component of the cell which is responsible for inducing acquired immunity. We do not know in the case of the tubercle bacillus which part of the cell this may be, but it is possible that by correlating the occurrence of a particular antibody with the occurrence of resistance, evidence might be gained on just this point. This is a well established immunological principle which is frequently neglected in the interpretation of immunity responses in the host.

In table 1 the antibody responses are noted simply on the basis of occurrence in groups of animals receiving the various preparations indicated; no evaluation is given here as to frequency of occurrence, and this may be misleading. Of the various antibodies found in the groups of animals in which they do occur, that to the protein is by far the one most frequently found. In these groups it is present in almost 100 per cent of animals. This is true also for serum reactivity with various types of whole bacillary antigens. Antibodies to wax occurred occasionally, and those to phosphatide less often, in those groups designated as positive. Antibody reactive with polysaccharide has been found in only one animal in about 200 tested.

The overall distribution of antibodies to bacillary components is thus greatest in animals immunized with BCG and heat-killed bacilli. When the individuals in these groups were examined, however, many of the most resistant of the BCG animals did not show antilipoidal antibodies, for example, whereas others with less marked resistance had these in measurable strength. In short, when we attempt to correlate these antibodies with the subsequent resistance to infection, it is obvious that no one of these antibodies, nor any combination of them, is related to resistance. It is of course possible that some other antigenic factor, as yet untested, may be involved, but these chemical fractions already tested represent the main components of the cell.

#### DISCUSSION

What we have to present now is an inroad into the examination of immunological reactions in tuberculosis on the basis of fractions of the tubercle bacillus. It may be worthy of repetition that only by establishing clear-cut relationships between host responses and bacillary components does it seem possible to avoid

the many controversial aspects of such concepts as acquired resistance in relation to allergy, the specific nature of the resistance mechanism, and related subjects. A complete analysis of this kind may prove to be impossible in the present state of chemical knowledge and methods, but it is deserving of a systematic study. The methods of pathology have yielded much to our understanding of the disease (3, 4), but these appear to have reached a plateau where personal interpretations by highly qualified observers are at variance, and this will continue until the overall aspects of the situation are reduced to their elements.

Our findings so far appear to dissociate the hypersensitive state from resistance by inducing the latter as an independent state with chemical components derived from the bacillus. If resistance can now be induced in the absence of hypersensitivity on a similar basis, it will be difficult to see how individual interpretation could seriously enter into the conclusions. It has not been possible definitely to establish that any of a variety of skin responses or humoral antibodies directed against components of the bacillus are related to the resistant state. This may mean that it rests on some response not measurable by present immunological methods, or that it is directed against one of the chemically minor portions of the microorganism.

Our plans are aimed toward an expansion of information along these lines, so that eventually we may be able to present a systematic survey of most of the chemical constituents of the bacillus, as well as of bacilli deprived of individual constituents, integrated with the immunological responses discussed above.

This report anticipates the future publication of the extended details of this and related work.

#### SUMMARY

Acquired resistance in tuberculosis cannot, at this time, be ascribed to any specific chemical portion of the tubercle bacillus. Attempts to establish such a relationship have included serological analysis employing the sera of resistant animals with chemical fractions of the bacillus, tissue responses to various isolated portions of the bacillus, and active immunization with such bacillary components.

The delayed type of tuberculin allergy has apparently been reproduced with isolated bacillary elements. The protein and wax of the human tubercle bacillus regularly induce reactivity to Old Tuberculin in guinea pigs. Although this demonstration is not yet complete, sufficient of the criteria have been satisfied to indicate that the hypersensitivity is the same as that consequent to the presence of whole tubercle bacilli in the tissues.

A preliminary experiment indicates that guinea pigs which have been rendered hypersensitive by means of isolated bacterial constituents do not develop resistance to infection with the tubercle bacillus. It is believed that this may provide the first immuno-chemical evidence for a distinction between hypersensitivity and immunity in tuberculosis.

## SUMARIO

A esta fecha no cabe imputar la resistencia adquirida a la tuberculosis a ninguna fracción química específica del bacilo tuberculoso. Los esfuerzos encaminados a establecer tal relación han comprendido: análisis serológicos empleando sueros de animales resistentes con fracciones químicas del bacilo, respuestas histológicas a varias porciones aisladas del bacilo e inmunización activa con esos componentes bacilares.

La forma tardía de la alergia tuberculínica ha sido aparentemente reproducida con elementos bacilares aislados. La proteína y la cera del bacilo tuberculoso humano evocan con regularidad reactividad a la Tuberculina Antigua en el cobayo. Aunque la demostración no es todavía completa, ya se ha cumplido una proporción suficiente de las pautas para indicar que la hipersensibilidad es idéntica a la consecutiva a la presencia de bacilos tuberculosos íntegros en los tejidos.

Un experimento preliminar indica que los cobayos hipersensibilizados por medio de componentes bacterianos aislados no manifiestan resistencia a la infección por el bacilo tuberculoso. Esto acaso aporte el primer dato inmunológico para diferenciar la hipersensibilidad y la inmunidad en la tuberculosis.

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# RESPIRATORY PATTERNS IN PULMONARY TUBERCULOSIS<sup>1</sup>

M. N. RAO AND LESLIE SILVERMAN<sup>2</sup>

In a recent article (1) we described a new type of pneumotachograph for recording the instantaneous rate and volume of air-flow during respiration.

This instrument consists of a section of straight tubing (31.6 mm. inside diameter) with an opening across the diameter of the tube. A fine platinum wire (10 $\mu$  in diameter and 200 mm. long) is suspended across the tube. The wire is encased in an air-tight housing and is pivoted at one end and fastened by a half-turn phosphor-bronze spring at the other end. The displacement of the wire is recorded photographically by a moving paper camera. Light from an arc lamp passes through small windows on either side of the tube parallel to the plane of the wire movement. The deflection of the wire is essentially linear with airflow and the inertia, lag and frequency of vibration do not interfere with respiratory measurements. Unlike other instruments devised for this purpose, this apparatus does not introduce significant resistance to airflow and, therefore, does not affect normal respiration.

The complete measuring apparatus consists of two instruments as described above, two minimal resistance valves (2), connecting tubing and a Heidbrink type face-piece. The instrument described above is modified slightly to permit expiratory airflow measurements since expiratory air is saturated with moisture and is in turbulent motion. These modifications are described in our article (Silverman, Lee and Drinker (3)) dealing with asthmatic patients.

A study of several asthmatic patients (3) indicated that the technique may be of diagnostic value in indicating pulmonary changes, such as bronchial constriction or loss of pulmonary elasticity. Because of the results obtained with asthmatic subjects, further studies upon other lung conditions was desirable. It was possible that certain pulmonary involvements where the injury was known, such as in poliomyelitis or in any paralysis of the diaphragm, such as following phrenic evulsion, might produce a definite respiratory pattern. In chronic or slowly developed diseases, such as tuberculosis or silicosis, there might be a concurrent change in the pattern of breathing with the progress of the disease.

There are several factors associated with respiratory conditions in tuberculosis which may alter the pattern of the breathing. Some of these factors are pleural adhesions and consolidation or operative procedures, such as artificial pneumothorax and thoracoplasty. To our knowledge no breathing studies of the type made possible by this apparatus have been reported for tuberculosis patients. The results of such a study of 8 well studied tuberculosis patients are presented in this article.

<sup>1</sup>From a thesis presented by M. N. Rao in partial fulfillment of the requirements for the degree of Doctor of Public Health, Harvard School of Public Health, Boston, Massachusetts.

<sup>2</sup>Assistant Professor of Industrial Hygiene, Harvard University School of Public Health, Boston, Massachusetts.

## EXPERIMENTAL

The patients used in this investigation are listed in table 1 with their physical condition at time of admission to the Sanatorium. Also noted is their condition just prior to our investigation with the laboratory air-flow apparatus. All patients were ambulatory and were made available for study through the kindness and coöperation of Dr. Francis P. Dawson, Acting Superintendent of the Middlesex Sanatorium, Waltham, Massachusetts.

TABLE 1

*Summary of clinical data on tuberculosis patients observed in this study*

SERIAL NUMBER	SUBJECT	RECORD NUMBER	AGE	SEDI-MENTATION RATE	VITAL CAPACITY	CLINICAL CONDITION AT ADMISSION (DATE IN BRACKETS)	CLINICAL CONDITION AT TIME OF EXAMINATION
			years	mm.	cc.		
1	J. S.	25	29	15	5,140	Far advanced (Aug., 1944)	A case for thoracoplasty
2	J. F. D.	27	53	42	1,900	Far advanced (Aug., 1944)	Slight improvement
3	W. McH.	28	25	30	4,300	Moderately advanced (July, 1944)	Progression of disease
4	L. L.	29	37	15	4,500	Moderately advanced (Nov., 1943)	Condition same
5	E. H. W.	30	50	50	2,475	Far advanced (Dec., 1943)	Slight improvement
6	W. W.	31	59	52	2,000	Far advanced (June, 1944)	No recent change
7	A. C.	32	42	40	1,550	Far advanced (May, 1943)	Slight improvement
8	J. McL.	33	53	50		Far advanced (April, 1944)	No change

Records were taken after the subjects had been sitting quietly for ten minutes. A record of at least eight respirations was then made. Inspiration and expiration resistances of 0.8 mm. of water per liter of air-flow per minute were added to the breathing circuit, without the knowledge of the subject, by means of adjustable resistances described in a recent article (4). After five minutes an 8-respiration record was obtained for this condition. The resistances were removed and another record was obtained after five minutes for comparison with the first taken with resistance to breathing.

## RESULTS

A portion of each of the minimal resistance curves on the 8 subjects are shown in figure 1. In addition to these curves a careful analysis was made of the records for maximum flow, minute volume, respiration rate, time to reach maximum inspiratory and maximum expiratory flow in per cent of the respective respiratory cycle. These values did not indicate a significant deviation from normal sub-

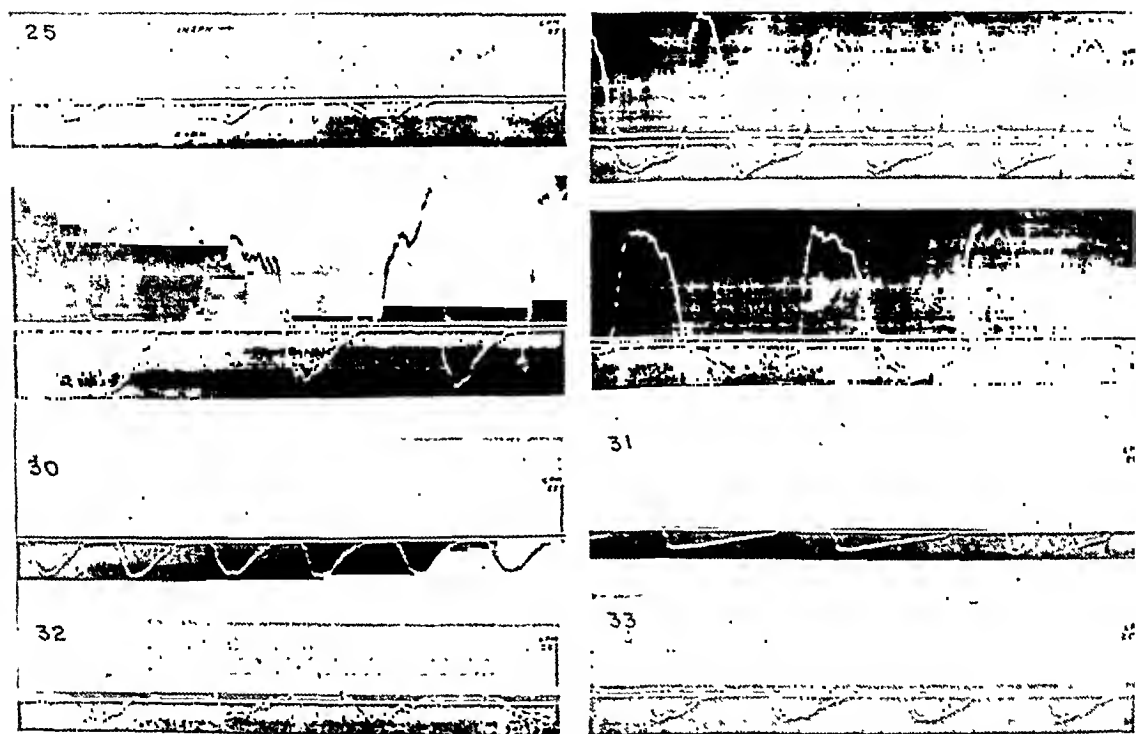


FIG. 1. Respiratory tracings (pneumotachograms) of 8 cases of pulmonary tuberculosis. Note the base line is inadvertently misplaced in records 30, 32 and 33. The upper curves represent inspiration, the lower expiration. The curves read from right to left. Time intervals one fifth second.

jects. The following observations on these patients and their respiratory curves (figure 1) are worth noting:

*Patient 1:* J. S., male, 29 years old at the time of examination. (Record 25, figure 1.) This patient was first diagnosed as having very mild tuberculosis in March, 1942. He entered the Sanatorium for a brief period and then was discharged. In August, 1944 he was readmitted with far advanced disease. A right pneumothorax was tried and abandoned. At the time the respiratory tracing was made he was being considered for thoracoplasty. This was completed later and he is still a patient at the Sanatorium.

X-ray diagnosis (film corresponds to period of above examination; March, 1945): Right lung field: mixed infiltration from apex to fifth rib; dense homogeneous shadows which may be fluid in the pleural cavity. A small cavity appears above the third rib. Left lung field: scattered fibrotic infiltration in the third interspace. Possibly some fluid in the right apex.

Analysis of respiratory tracing: Record 25 represents a normal type of curve with characteristic jerky motions during inspiration and expiration. The upper portion of the curve represents inspiration and the lower, expiration.

*Patient 2:* J. F. D., male, 52 years at the time of examination. (Record 27, figure 1.) This patient entered the Sanatorium in January, 1941, after diagnosis of far advanced tuberculosis. He refused pneumothorax treatment and was considered a poor risk for thoracoplasty. After bed-rest the patient was discharged in April, 1942. He was re-admitted in August, 1944, and again received bed-rest until May, 1945, when he was discharged. He is now under observation in the out-patient clinic and appears to be in a satisfactory condition at the present time (May, 1946).

X-ray diagnosis (film taken on first examination, December 30, 1940): Right lung field: mixed infiltration, upper half of lung; irregular areas of decreased density suggesting honeycomb cavitation. Left lung field: scattered and diffuse infiltrations through entire lung of a mottled character. Emphysema at both bases.

X-ray film taken at time respiratory tracing was made (shown in figure 2). This plate shows that in the right lung there is a spread of the disease throughout the entire lung field which is very marked in the upper lobe. A poorly defined cavitation and fluid are present. In general this patient is a good example of early fibrosis and progressing to excavation. The trachea has been displaced in the process.

Analysis of respiratory tracing: Record 27 appears normal during inspiration, but there is obvious damping and a sudden drop in flow at the end of the expiratory phase of the cycle. This shape of curve was observed previously in known cases of asthma (3) and recently in observation on silicotic patients. No history of either disease was indicated in this patient.

*Patient 3:* W. McH., male, 24 years at the time of examination. (Record 28, figure 1.) When diagnosed in March, 1943, this patient had mild disease. In July, 1944 the disease showed moderate advancement and the patient was admitted to the Sanatorium. A left pneumothorax was unsuccessful and the patient was given bed-rest until discharged in August, 1945.

X-ray diagnosis (film corresponding to above tracing): Right lung field: normal. Left lung field: slight progression of the disease.

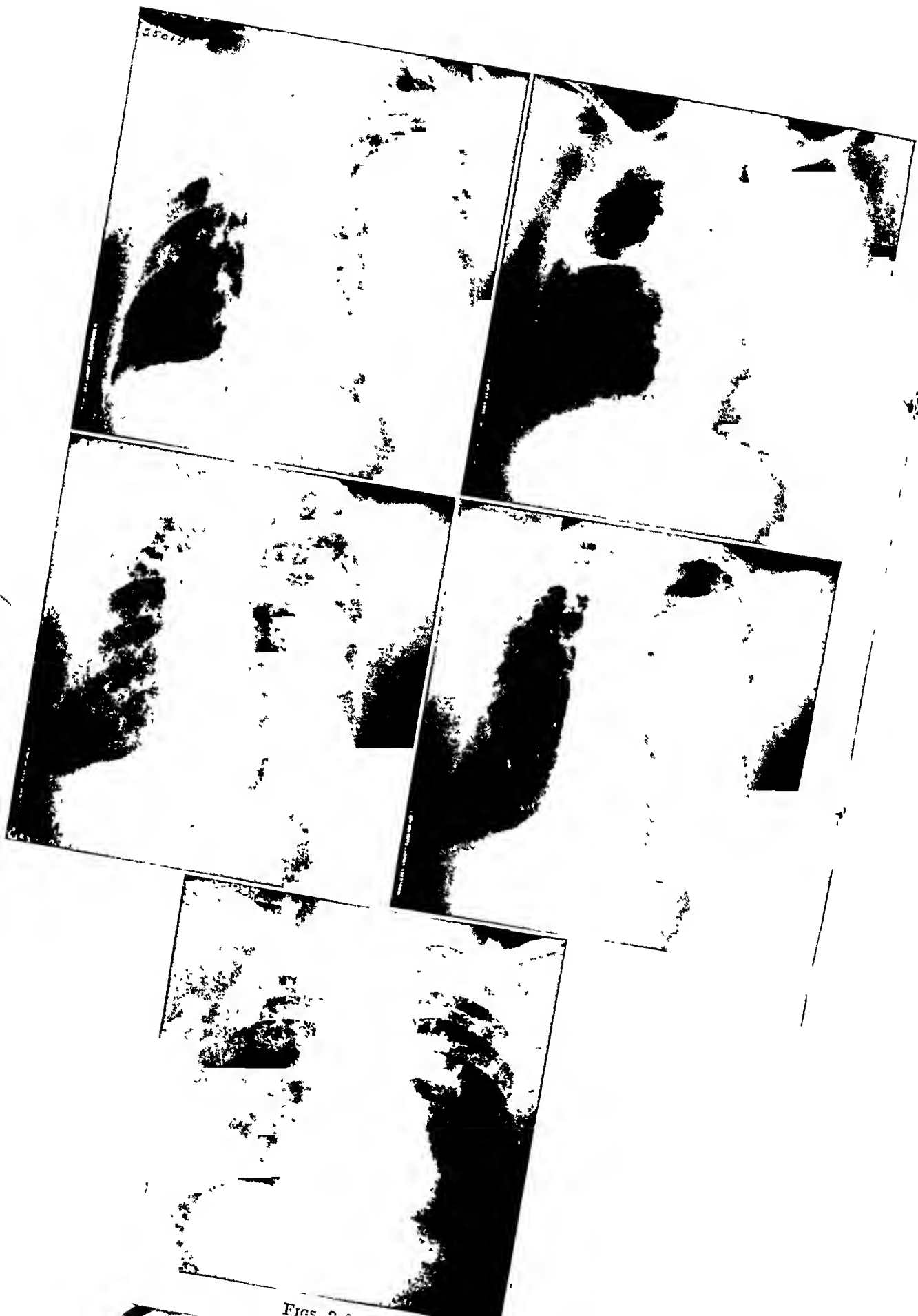
Analysis of respiratory tracing: Record 28 is that of a very irregular breather with no characteristic deviation from normal.

*Patient 4:* L. L., male, 38 years at the time of examination. (Record 29, figure 1.) This man was first rejected by the Army for selective service in May, 1942. In November, 1943 he was admitted to the Sanatorium and his condition was diagnosed as moderately advanced tuberculosis. Since our examination he has refused artificial pneumothorax treatment and in May, 1946 was bronchoscoped. A persistent positive sputum is still present.

X-ray diagnosis (film on admission, November 24, 1943): Right lung field: normal. Left lung field: some progression of disease. Film at time of respiratory tracing (March 21, 1945): No appreciable change from above. Questionable progression of disease in right lung. No fibrosis or emphysema is present.

Analysis of respiratory tracing: Record 29 appears normal except that the expiratory curve is almost interrupted halfway through the cycle. Complete interruption in this phase of the cycle has been seen in patients with bronchial spasm.





Figs. 2-6

*Patient 5:* E. H. W., male, 45 years at the time of examination. (Record 30, figure 1.) The first diagnosis of disease in this patient was made in April, 1943. He was admitted to the Sanatorium in April, 1943, with a diagnosis of moderately advanced disease. After a month he was discharged and observed in the out-patient department where his X-ray film showed progression and he was readmitted in December, 1943. At this time his sedimentation rate was 60 mm. (Wintrobe), but by the time the respiratory tracing was made this had dropped to 50. Hemorrhages started late in October, 1945, and the patient died November 14, 1945. At the time the respiratory tracing was made he had no complaints.

X-ray diagnosis (film taken on February 21, 1945, just prior to respiratory tracing): Right lung field: a large cavity is present in the upper portion. (See figure 3). In the first plate obtained on this patient some fibrosis was evident in this area. Left lung field: normal.

Analysis of respiratory tracing: Record 30 indicates that some damping is present in the expiratory phase of the respiratory curves as shown by the smoothing and rounding of the curves. (The base lines were unfortunately displaced during the recording.)

*Patient 6:* W. W., male, 57 years at the time of examination. (Record 31, figure 1.) This patient entered the Sanatorium in June, 1944. In 1941 he was diagnosed as tuberculous and bed-rest at home was advised. On admission he had a bad cough, positive sputum and far advanced disease. A right pneumothorax was tried and abandoned and he was not recommended for thoracoplasty. In November, 1945 his sputum became negative and after bed-rest he was discharged in April, 1946.

X-ray diagnosis (film on admission, June 17, 1944, figure 4): Right lung field: mixed infiltration in the upper lobe. Linear markings accentuated throughout the remainder of the lung field. A cavity containing fluid and approximately 5 cm. in diameter is present behind the second rib. The diaphragm is flattened and probably adherent laterally on the right. The trachea is markedly displaced to the right. Left lung field: mixed infiltration from apex to third interspace.

Film at time of respiratory tracing (April 3, 1945, figure 5) showed contraction of the cavity in the right lung. A plate taken just before discharge indicated that the cavity is less distinct and the left lung is unchanged.

This patient closed a cavity by fibrosis, which is confirmed by the sputum change from positive to negative, and also by X-ray observations.

Analysis of respiratory tracing: Record 31 presents an inspiratory curve which is not abnormal, but the expiratory curve is typical of a damped lung movement, such as that produced in asthma, emphysema or silicosis. The marked turbulence in the last respiration may be due to a spasm.

*Patient 7:* A. C., male, 43 years at the time of examination. (Record 32, figure 1.) This patient was well until 1942, when he began to cough and bring up blood. He was

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FIG. 2. (Upper left) Patient J. F. D. (Record 27, figure 1) X-ray film corresponding to period respiratory tracing was obtained.

FIG. 3. (Upper right) Patient E. H. W. (Record 30, figure 1) X-ray film corresponding to period just prior to respiratory tracing.

FIG. 4. (Centre left) Patient W. W. (Record 31, figure 1) X-ray film on admission to Sanatorium.

FIG. 5. (Centre right) Patient W. W. (Record 31, figure 1) X-ray film corresponding to period respiratory tracing was obtained.

FIG. 6. (Lower) Patient J. McL. (Record 33, figure 1) X-ray film corresponding to period of respiratory tracing.

admitted to the Sanatorium in May, 1943, after diagnosis of far advanced disease. A left pneumothorax was tried and abandoned, and a right one was unsuccessful. In November, 1943 a thoracoplasty was performed and 10 ribs were removed. His sputum is still negative (May, 1946).

X-ray diagnosis (film on admission, May 17, 1943): Right lung field: mixed infiltration with nodular fibrosis in the region of the third rib. A cavity is present in the right apex. Left lung field: mixed infiltration from apex to sixth rib.

An X-ray film in March, 1945, at the time the respiratory tracing was made, showed little progression of the disease.

Analysis of respiratory tracing: Record 32 appears normal in configuration but a considerable amount of turbulence is evident in both phases of the cycle. This turbulence may be attributed to an exaggerated respiratory reflex or apprehension.

*Patient 8:* J. McL., male, 52 years at the time of examination. (Record 33, figure 1.) This patient was admitted to the Sanatorium in April, 1944, with a positive sputum and for advanced disease. He was put on bed-rest and was discharged in April, 1945, at his own request.

X-ray diagnosis (film taken at time of admission, April 25, 1944): Right lung field: mixed infiltration, shallow cavities, trachea retracted to the right. Left lung field: mixed infiltration in upper lobe, possible adhesion to diaphragm and some fibrosis are evident.

Film taken at time of respiratory tracing (April 2, 1945), and shown in figure 6, shows no change.

Analysis of respiratory tracing: Record 33 appears normal.

#### DISCUSSION

From the above results it is apparent that 3 of the 8 cases exhibit deviations from normal respiratory air-flow curves. These abnormal records indicate the presence of an increased resistance in the bronchial passages or perhaps some loss in elasticity of the lung tissue. Bronchial resistance might be caused in these cases by exudation of mucus, but it seems more likely that a significant amount of fibrosis causes the abnormal curve.

Of the 8 patients examined, 4 have significant fibrosis as shown by X-ray. One patient, no. 2, J. F. D., also has emphysema at the base of both lungs. Emphysematous patients have been found to exhibit markedly damped curves, the degree of damping depending upon the amount of emphysema. One patient with an X-ray diagnosis of fibrosis and possible adhesion to the diaphragm (no. 8, J. McL.) failed to show any demonstrable change in the tracing of the respiratory air-flow. This patient has chronic disease and may have enough reserve pulmonary surface so that his involvement was not sufficient to alter the breathing curve. Three of 4 X-ray diagnoses are therefore confirmed by means of tracings of the respiratory air-flow.

The addition of inspiratory and expiratory resistance in all of these cases caused a diminished minute volume and a reduced maximum flow in both phases of the cycle. The majority of normal persons also react similarly, but the reduction in the patients with pulmonary tuberculosis is greater than in normal subjects.

## SUMMARY

This investigation was made to observe patterns of respiration in 8 tuberculosis patients with a new type of minimal resistance pneumotachograph. Three of the 8 patients exhibited damped curves similar to those observed in asthmatics. On the basis of the X-ray diagnoses, 4 patients might be expected to show changes in the respiratory air-flow curves. A significant reduction in minute volume as compared to normal subjects was noted when external resistance to both phases of respiration was placed in the breathing circuit.

## SUMARIO

Llevóse a cabo esta investigación para observar, con un nuevo tipo de pneumotacógrafo de resistencia mínima, el desenvolvimiento de la respiración en 8 tuberculosos. Tres de los 8 manifestaron curvas deprimidas como las que se observan en los asmáticos. A base del diagnóstico roentgenológico, cabía esperar que 4 enfermos mostraran alteraciones en las curvas del aire inhalado. Observóse una disminución significativa en el volumen por minuto, comparado con el de sujetos normales, cuando se colocaba en el circuito respiratorio la resistencia externa a ambas fases de la respiración.

*Acknowledgments*

Patients for this study were made available through the assistance of Dr. Alton S. Pope of the Massachusetts Department of Public Health, and Dr. Francis P. Dawson, Acting Superintendent, Middlesex Sanatorium, Waltham, Massachusetts. Dr. Dawson also furnished the case histories and X-ray material. Their aid is gratefully acknowledged.

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## EDITORIAL

### On the Etiology of Sarcoidosis

Sarcoidosis has become a much discussed disease in the American literature since the paper by Longcope and Pierson in 1937 drew attention to it. Up to that time fewer reports had appeared in the entire American literature than have been published every year since. There is now evidence of a trend to overdiagnose sarcoidosis, not only clinically and roentgenologically, but histologically as well.

Although several different opinions on its etiology have been discussed, here and abroad, it is probably fair to say that nobody has been able to prove his theory convincingly, even to his own complete satisfaction. The most prudent, although not the most fertile attitude is that which declares that the etiology is unknown. Of all authors who have expressed a positive opinion, those who believe that the tubercle bacillus is directly or indirectly involved in the etiology are a majority. The writer is one of that majority and has tried to show that this hypothesis is plausible, and that—as is implicit in the meaning of “hypothesis”—it is not in apparent conflict with known facts and may furnish suitable ground for further investigation. He has also attempted to show which clinical and morphological syndromes are comprised in the broad term sarcoidosis. Parenthetically, and misquotations notwithstanding, he has never believed that an acceptable proof of this hypothesis has ever been presented by him or by anybody else.

A large part of the etiological discussions have revolved around the strictly bacteriological proof in the classical sense of Koch's postulates. However, the problem is unfortunately a good deal more complicated than that, and it may be worth while to point out some of the actual methodological complexities.

It is agreed that true tuberculosis and sarcoidosis coexist not infrequently, particularly in patients who are carefully and completely studied postmortem. It is also quite generally recognized that occasional small areas of caseous necrosis are frequently found in otherwise perfectly typical cases of sarcoidosis. The purist opinion would exclude such cases from the diagnosis, because it is considered a part of the diagnostic definition that sarcoid tubercles do not caseate. The justification for such strict criteria appears questionable in the light of broad clinical and pathological observation. But, even if the strictest diagnostic criteria be accepted, they account for only those cases in which necrotic foci *are found* and quite obviously not for the unquestionably numerous cases in which they are present but are *not found*. Since sarcoidosis is characteristically a disease with innumerable disseminated foci, the absence of caseation is beyond the possibility of scientific proof in any given case.

This morphological reality makes a future bacteriological proof—*pro* or *contra*—appear hopeless. Let us assume that improved methods will demonstrate tubercle bacilli much more frequently in sarcoid tubercles than has been possible in the past. Then, the proponent of the tuberculosis etiology will have no better

answer than he has now for the interpretation of his opponent that the finding of tubercle bacilli merely proves that caseous foci must be present, belonging by definition to a coincidental true tuberculosis, be it ever so minimal in extent. In other words, the mere demonstration of tubercle bacilli in secretions or in occasional sarcoid foci will not necessarily change the opinion of the worker who, for a multiplicity of reasons, is convinced that sarcoidosis is not caused by the tubercle bacillus. It would then seem that the correctness of the hypothesis that sarcoidosis is a phase of tuberculosis is not likely to be solved by strictly bacteriological studies, but must depend on a broader or on an entirely new approach.

On the other hand, the advocate of the tuberculosis etiology will probably continue to be not too much impressed by the failure of finding tubercle bacilli. He will point out that such failure is not as powerful an argument as it is often made out to be. If Koch's postulates were applied to the diagnosis of all tuberculous lesions, the correct diagnosis could not be made in many instances, in which it is not in doubt. A vast majority of all more or less healed primary foci, as well as their lymph node components, do not contain any tubercle bacilli, demonstrable by any available technique. The same is true of many postprimary foci, particularly if they are small and disseminated. Even young productive tubercles, at times, do not harbor demonstrable tubercle bacilli. Furthermore, many experimental observations are on record which prove the dying out of bacilli in tuberculous foci, frequently at a developmental stage at which the histological characteristics of such lesions are still obvious. It is significant that a rapid decrease of the bacillary population is likely to occur coincident with the maturation of epithelioid cells. In this connection it may be recalled that, out of the great many attempts to demonstrate tubercle bacilli in sarcoid lesions, one particular study deserves more attention than most of the other ones. I refer to the work by Kyrle, who found many acid-fast bacilli in clinically very young skin lesions before they showed the histologically characteristic picture; the same foci, as they matured to the typical epithelioid tubercle, were free of acid-fast bacilli. This unique study is not fully convincing, just because it is unique; but it indicates a potentially successful approach. It is entirely possible that the very nature of sarcoidosis is the purely epithelioid response to tubercle bacilli, the immunological aspect of which is the rapid disintegration of the bacilli which caused the epithelioid reaction. If this be so, recent attempts to prove that sarcoidosis has no relation to tuberculosis, because it is not associated with some immuno-biological constellations commonly present in tuberculosis, lose their meaning in etiological discussion.

Some experiences which I have gathered since the publication of my literature review on sarcoidosis in 1938 have taught me the desirability of differentiating between sarcoid and sarcoidosis. The latter term should be reserved for the disease with its disseminated foci. The former term, used as an adjective, should describe the histologically characteristic structure. The significance of the differentiation is twofold: (1) As mentioned in my review, sarcoid structures have been produced in patients with sarcoidosis by the injection of non-

specific material. (2) I have seen in a few cases one single sarcoid tubercle as an accidental postmortem finding in patients who had neither tuberculosis nor sarcoidosis. One or two single but diagnostically unquestionable foci certainly do not justify the diagnosis of sarcoidosis, which is a systemic disease. The pathologist who is confronted with a biopsy specimen containing a few characteristic sarcoid tubercles should probably report no more than "sarcoid tubercles;" he cannot know whether the patient has sarcoidosis. If such single lesions are included in the diagnosis sarcoidosis, the etiological problem becomes needlessly complicated. It is also pertinent to recall that the clinical and roentgenological diagnosis of sarcoidosis is beset with difficulties and uncertainties. The appearance of the chest roentgenogram is suggestive at best, but not pathognomonic. It is even conceivable that disseminated pulmonary lesions are not due to sarcoidosis in some patients in whom biopsies of lymph nodes contain sarcoid structures. The etiological problem is further complicated by the probability that histologically characteristic lesions may be caused by agents other than that unknown  $x$  that causes sarcoidosis. In other words, it is quite possible, or even probable, that the characteristic structural entity sarcoidosis may be caused by more than one etiological agent.

In the present stage of our knowledge, it would seem wiser to recognize clearly the complexities that confront etiological studies and the methodological limits of our present working tools than to insist on any one etiological hypothesis, including the agnostic one that claims that the etiology is unknown.

MAX PINNER

## Leroy A. Gardner

December 9, 1888–October 24, 1946

The sudden death of Doctor Gardner from coronary thrombosis brought a grievous shock to his many friends and associates. He was the authority on diseases due to dust, notably silicosis, and in constant demand for advice in relation to dust hazards in industry.

Born in Connecticut, educated in the schools of Meriden, he was given an A.B. by Yale University in 1912, M.D. in 1914, and an honorary M.Sc. from the same institution in 1939.

Following his graduation in medicine he entered Boston City Hospital as an intern in pathology under the elder Mallory, and at Harvard Medical School was instructor in pathology. In 1917 he became Assistant Professor of Pathology at Yale. Shortly afterward at Camp Devens, where he was a Lieutenant in the Army Medical Service, he developed tuberculosis and came to the Trudeau Sanatorium. In April, 1918 he was well enough to enter the Saranac Laboratory on a Fellowship of the Trudeau Foundation. He became interested in the study of dust inhalation in connection with tuberculosis, especially in the excessive death rate from the disease among granite cutters in Barre, Vermont and elsewhere. The contrast between the mortality among marble and granite cutters was the basis of much experimentation, which led to his demonstration that it was silica in the granite that was the cause of activation of latent tuberculosis and a potent cause of progressive disease.

This outstanding contribution to the knowledge of silicosis was of fundamental importance and Doctor Gardner became widely recognized as an authority on the subject.

As a result of further painstaking study he widened our knowledge of the hazards of dusts in industry and was in demand as consultant by many industries as well as governmental agencies in the United States.

In 1927 he became Director of the Saranac Laboratory and in 1938 was made Director of the Edward L. Trudeau Foundation and a Trustee of the Trudeau Sanatorium. He was pathologist for the local hospitals and for the Veterans Hospital at Sunmount, New York, and Lecturer in Medicine at the University of Rochester.

As the quality of his work became better known, various honors were given to him. The National Tuberculosis Association awarded him the Trudeau Medal in 1935 for his work in disease due to dust, and the American Association of Industrial Physicians and Surgeons gave him the Knudsen Award for outstanding achievement in industrial medicine in 1940. His memberships in many medical societies included the American Association of Pathologists and Bacteriologists; the American Society for Experimental Pathology; the Council on Industrial Health of the American Medical Association. The energy and genius of Doctor Gardner were responsible for a surprising amount of very important research.

The consultation services of Doctor Gardner and his staff to industries in the



United States and abroad have not only shed light on the nature of the various dust hazards which confront them, but developed successful methods of prevention and control. As one indication of his eminence in this field, he was selected in 1930 as one of the two delegates from the United States Government to the International Conference on Silicosis in South Africa, where he was elected secretary of the medical division. He also represented the Government at the International Labor Conference on Pneumonokoniosis in London in 1932 and



Leroy U. Gardner  
1888-1946

again at Geneva, Switzerland, in 1938. He served for several years as Special Consultant to the United States Public Health Service.

He arranged and conducted four Symposia on Silicosis, held at the Saranac Laboratory in 1934, 1936, 1937 and 1939, and one on Tuberculosis in Industry in 1941.

In this country research into the relationship of silicosis to tuberculosis has centered in the Saranac Laboratory. Thus there have developed many experiments of great importance to industry, and these have led to new state laws to safeguard employees and for compensation for disability. He published more than fifty studies besides a volume on *Tuberculosis: Pathology, Bacteriology*

and *Laboratory Diagnosis* in association with Baldwin and Petroff. He was a member of the Editorial Board of the *American Review of Tuberculosis* since 1938.

It is fitting to add some tribute to Doctor Gardner's capacity for friendship. He was respected and beloved by all who knew him well and especially by his medical associates in Saranac Lake. A devoted husband and father of two daughters, he also found time to help in local affairs as a Trustee of Saranac Lake Village and President of the Board of Water Commissioners. He served as a Trustee of the Presbyterian Church and joined in many activities for the betterment of the community. His loss to the scientific world is such as to challenge all in similar research to follow his example; his loss to those closest to him is heart-breaking.

EDWARD R. BALDWIN

*Biographical Data*

LEROY U. GARDNER

Born New Britain, Connecticut, December 9, 1888

Son of Irving Isaac and Inez Baldwin (Upton) Gardner

B.A., Yale, 1912; M.D., 1914

Graduate study Boston City Hospital and Harvard Medical School, 1914-1917

Married Carabelle McKenzie, June 22, 1915; children Margaret, Dorothy

Instructor in pathology, Harvard Medical School, 1916-1917

Assistant professor of pathology, Yale School of Medicine, 1917-1918

Pathologist, Trudeau Foundation, Saranac Lake, New York, 1919-1927

Director of laboratories, same, since 1936

Director, Saranac Laboratory for Study of Tuberculosis, since 1927

Lecturer in medicine, University of Rochester

Served as Lieutenant, Medical Corps, U. S. Army, 1917

Trustee, Village of Saranac Lake, 1932-1933

Member Water Board, same, 1929-1930

Member Village Planning Commission

Trustee of Trudeau Sanatorium

Director, Trudeau Foundation, since 1938

Member Correlating Committee on Silicosis, International Labor Office, 1932

Fellow, American Association for the Advancement of Science

Member, American Association of Pathologists and Bacteriologists

Member, National Tuberculosis Association (Board of Directors)

Member, Editorial Board, *American Review of Tuberculosis*, since 1938

Fellow, American Medical Association (Council on Industrial Health)

Trustee and member, Medical Committee, Industrial Hygiene Foundation of America

Charter member, American Academy of Industrial Medicine, 1946

Beta Theta Pi, Nu Sigma Nu

Republican; Presbyterian

Author "Tuberculosis—Bacteriology, Pathology and Laboratory Diagnosis," with E. R. Baldwin and S. A. Petroff, 1927

Contributor to medical publications on silicosis and related disease due to dust

Home: 36 Old Military Road, Saranac Lake, New York

## BOOKS

MANUEL TAPIA: *Formas Anatomoclínicas, Diagnóstico y Tratamiento de la Tuberculosis Pulmonar. Volume 1. Second corrected and considerably enlarged edition. Pp. 503, with 492 illustrations, Livraria Luso-Espanhola, Lda., Rua Novo do Almado, Lisboa, 1945, paper.*

By WILHELM SWIENTY

Doctor Tapia has based his book upon material which he observed in Spain and Portugal. The purpose of the book is to describe representative cases of all types of pulmonary tuberculosis in all their aspects, some including anatomical findings. Each case is thoroughly discussed and similar cases from the literature are cited and compared.

Herein lie the advantage and the disadvantage of the book. While it is necessary to study and discuss personal experiences, especially in such an immense material as Dr. Tapia presents, it may have been of greater benefit to the reader if he had selected fewer typical and atypical cases and not presented so many similar cases.

To the confusing multitude of classifications of pulmonary tuberculosis, Dr. Tapia adds one of his own. He distinguishes between three main types: primary infection, reinfection and pleural tuberculosis. As involvement of the pleura is so common, Dr. Tapia believes it deserves a place as a main group in his classification. His subdivisions are numerous. Sometimes a new and, at times bewildering terminology is used. Although his classification is exhaustive, there are many others which have been more generally accepted. It seems to this reviewer that there is no need of a new and rather debatable classification. It only proves once more the urgent need of an internationally recognized standard of classification of pulmonary tuberculosis which would greatly simplify the scientific and practical work in this field.

The book is patterned after that classification. A short historical review is given at the beginning of each chapter. The German and French literature has been exhaustively referred to, whereas many of the recent Anglo-American publications have been ignored. The chapters on primary tuberculosis are especially well written. The history of each case is given in detail. Much emphasis is put on the interpretation of the X-ray findings in comparison with the physical signs. Each case is discussed as to differential diagnosis and treatment and is illustrated by a series of roentgenograms (positives) which are of the highest technical standard. The diagrams also are excellent.

This first volume covers the primary type of infection and part of the reinfection type of tuberculosis. It is amazing that nowhere bronchoscopic examinations are reported in spite of their great value in securing a diagnosis of bronchial involvement and in establishing the form of treatment. This absence of bronchoscopic findings makes it difficult to follow the author in certain polemics as he sometimes lacks proof of his assertions, especially in the chapters about the

coexistence of primary and secondary infiltrations. The maintenance of the term "epituberculosis" is unfortunate. The treatment of atelectatic lesions without the benefit of bronchoscopy must, by necessity, be indiscriminate. Only in very rare instances has the author used tomography and bronchography.

There is but scant reference to modern surgical collapse treatment of tuberculosis. There are many typographical errors, including misspelling of Robert Koch's name. The lack of a bibliographical index adds to the difficulty in reading this book. With its abundance of material, it is recommended for those specialists who are primarily interested in case reports and X-ray studies.

ANDREW LADISLAUS BANYAI: *Pneumoperitoneum Treatment*. Pp. 376, with 74 illustrations, St. Louis, The C. V. Mosby Company, 1946, cloth, \$6.50.

By MAX PINNER

Doctor Banyai's book on *Pneumoperitoneum Treatment* is, for one thing, a broad and most meticulous compilation of the literature on this subject plus many topics of only marginal pertinence to the central theme. It is not likely that any publication of significance to this topic was overlooked. The compilation was done with scholarly accuracy and scholastic completeness in which the reader may sometimes miss the author's guidance and discrimination between the solid and the mere speculative contributions, between sound practice and more or less obvious fads. It seems implied in the arrangement and style of the book, although it is not explicitly stated, that encyclopedic completeness is the aim, rather than an expression of the author's opinions. The present status of pneumoperitoneum, particularly as a form of collapse therapy for pulmonary tuberculosis, makes Doctor Banyai's choice appear appropriate and wise. Although pneumoperitoneum has a history of over fifty years as a treatment of peritonitis and a somewhat shorter one as a treatment of tuberculous enterocolitis, as Doctor Banyai points out in his brief historical account, its use in the treatment for pulmonary tuberculosis is little older than one decade, obviously too short a time for definitive indications, contraindications and results. However, since pneumoperitoneum is apparently being used more and more, a competent discussion of its mechanical and physiological effects is timely and an important basis for future clinical work. Since Doctor Banyai was the first to recommend pneumoperitoneum for the treatment of pulmonary tuberculosis and since he has so prominently contributed to the clarification of its physiological effects, he was eminently qualified to have written the first large monographic study. He presents his own physiological observations and the physical effects of pneumoperitoneum in great detail. It would be preferable had he chosen to use exclusively the accepted physical terms for the description of physical conditions.

One may question whether the time chosen for such a first major survey is entirely felicitous. The answer may well be yes for the first 170 pages, in which the basic physiological aspects are discussed with the competence of first-hand

knowledge. These first 170 pages contain also the fairly generally accepted indications for pneumoperitoneum in the treatment of tuberculous peritonitis and entero-colitis, the possible complications of the procedure and its technique.

The next 130 pages are devoted to pneumoperitoneum as treatment for pulmonary tuberculosis, and for this chapter the time for publication is rather unfortunate, because there is little doubt that within the next two or three years more and larger series of cases will be published than Doctor Banyai had at his disposal from his own experience and from the literature. As it is, this chapter, and especially the nearly 60 pages on therapeutic results, is by necessity disappointing and but little informative. The largest series of cases reported before the completion of Doctor Banyai's manuscript were: 250 cases by Trimble; 200 by Bennett; 101 by Rilance and Warring; 156 cases by Mallick and associates. These are the only reports available to Doctor Banyai, based on more than 100 patients. Even these reports do not contain statistically significant numbers of *final* results. The vast majority of all other reports analyzed by Doctor Banyai are based on well below 50 cases, each. Since Doctor Banyai wrote his book, two papers with a total of over 600 patients have appeared in the REVIEW alone and Dr. R. S. Mitchell and coworkers of the North Carolina Sanatorium have just submitted a report on more than 700 patients.

It is difficult to gain an accurate picture of the present use of pneumoperitoneum. Drolet, in 1943, reported that, of 99 Canadian and American Tuberculosis Hospitals and Sanatoria, only 44 used this form of treatment at all during the five years 1937 to 1941. However, he states that the number of patients so treated annually increased from 179 to 352. Some institutions have abandoned pneumoperitoneum following disappointing experiences, some have enormously increased its use under the impetus of a therapeutic optimism which is still sorely in need of statistical justification. Increased use implies, of course, broadened indications far beyond the cautious recommendations in Doctor Banyai's book. In some clinics, pneumoperitoneum has become a treatment of choice for many patients, mainly because the dreaded pleural complications of pneumothorax are avoided. It is also being used in many patients with minimal lesions in whom other phthisiotherapists would recommend only bed-rest. The pendulum swings into extremes. There is no other treatment for pulmonary tuberculosis at the present time, even including pulmonary resection, in which competent opinions are so far apart as in the indications for pneumoperitoneum. The psychic effects of pneumoperitoneum should be assessed. Air-refills at brief intervals help to retain control over patients and provide regular medical supervision, which in itself is part of any treatment. Since refills are advised over periods of years, this aspect of pneumoperitoneum therapy is important, although its beneficial effects cannot be ascribed to the procedure *per se*.

It will take years and careful, unbiased study before pneumoperitoneum will reach a state of relative balance, such as pneumothorax and thoracoplasty have apparently gained. Doctor Banyai's book will unfortunately not play an important rôle in this discussion, because it contains extremely little information on final therapeutic results and because the author does not present his own observa-

tions in a numerically usable fashion; but his reticence is understandable and probably justified. Out of some 70 roentgenograms, only 29, representing 10 patients, are shown as illustrations for the therapeutic effectiveness of pneumoperitoneum in pulmonary tuberculosis. Of these 10 patients, 4 were still under treatment at the date of the last roentgenograms and only 2 films were taken more than two months following cessation of treatment.

As indicated in a former paragraph, developments in the use of pneumoperitoneum have been so rapid during the last few years that many observations have not yet been published, so that some questions of the clinical application of pneumoperitoneum are already beyond the stage discussed in Doctor Banyai's book. This is true, at least in some clinics, for indications, as already mentioned. As far as contraindications are concerned, it seems of great interest to mention (with the kind permission of the authors) that Drs. Mitchell, Hiatt, McCain, Easom and Thomas have observed that the diaphragm remains completely paralyzed in nearly 50 per cent of patients treated by phrenic crushing plus pneumoperitoneum, while this holds true for only 24 per cent of patients in whom phrenic crushing was not combined with pneumoperitoneum.

The remaining 8 chapters, comprising nearly 150 pages, deal with the application of pneumoperitoneum in a great variety of other morbid conditions, such as postoperative intraperitoneal adhesions, abdominal pain following pneumothorax refills, vomiting of pregnancy, bronchitis, tuberculous empyema, tuberculous salpingitis, pulmonary abscess, bronchial asthma, bronchiectasis, pulmonary emphysema, etc. It is particularly in regard to some of these therapeutic claims, some of which are hard on the reader's credulity, that this reviewer would have wished for more evidence of Doctor Banyai's criticism. The fact that he reports in equal detail some papers containing fantastic indications and results, as he does obviously valid observations, may too readily, although unjustifiedly, be interpreted as approval or agreement.

In spite of the generous size of the roentgenograms, the majority of reproductions are poor, because an unusually coarse grain is evident in some (for example, 25, 37, 39, 67, 68), and because contrast is so poor as to obliterate roentgenological details in others (as 27, 28, 30, 59), leaving a small number that are technically and esthetically satisfactory. The author must have recognized this deficiency, because he makes profuse use of arrows and lines to point out details that roentgenographic reproductions should clearly show without such artificial aids. Otherwise, the publisher is to be congratulated on the physical appearance of the book. An author index is missed, particularly since the long bibliographical list does not contain any reference to the pages on which the papers are mentioned, which diminishes its practical usefulness.

HAROLD HOLAND: *Rehabilitation at Lake Tomahawk State Camp. A History.* Pp. vii + 46, published by the National Tuberculosis Association, 1790 Broadway, New York, 19, N. Y., 1945, cloth.

By LOUIS D. SILTZBACH

The State of Wisconsin, always a pioneer in social legislation, set up Lake Toma-

hawk State Camp as an experimental project for the rehabilitation of the tuberculous in 1915. At that time there was great interest in a state reforestation program and, since a cold dry climate was considered optimal for the treatment of pulmonary tuberculosis, it was decided to send convalescent sanatorium patients to help reclaim the northern woods.

In this booklet Mr. Harold Holand, director of the Research Department of the Wisconsin Anti-Tuberculosis Association, gives us an historical account of the Camp's development from 1915 to 1940. He tells the story simply and engagingly. He writes of the legislative hurdles which had to be cleared at the Camp's initiation, of the scrambling for funds to keep going, of the efforts to keep the legislative authorities and the public convinced of the usefulness of a post-sanatorium period of work adjustment and, finally, of the feeling of accomplishment that warmed the founders as they watched the project take root and blossom.

Quickly it became evident that forestry and logging were too arduous for most patients; so, over the years, the Camp was transformed into a farm colony. Light tasks in animal husbandry, poultry raising, landscaping and greenhouse work were assigned. An industrial workshop and school facilities were later set up for vocational training and academic courses. The Camp's power plant and other maintenance units were used increasingly for practical training purposes.

Since the mid-thirties, the admission criteria have been the following: Lesions arrested or apparently arrested; tolerance for one or two hours' daily exercise; and good prognosis of becoming self-supporting. About half the patients admitted in the last decade have had far advanced disease. From 1915 to 1939, the Camp discharged 812 persons alive after an average stay of 9.8 months. At present the Camp accomodates 48 patients; only males are accepted.

Although the author is primarily concerned with the Camp's history, he includes some tables to give an approximate picture of results achieved. He is aware of the lack of a true non-rehabilitated control group and therefore restricts his analyses to comparisons between the outcome among fully rehabilitated patients and those partially rehabilitated. The overall follow-up results among the total group, which was observed from one to twenty-five years after discharge from the Camp, are very good. On the closing date of observation, May, 1940, 71 per cent were living, 17 per cent were dead and 12 per cent could not be traced.

There was considerable difference between the mortality of patients graduated as fully rehabilitated—60 per cent of the total admitted—and that of patients who left as partially rehabilitated—28 per cent of those admitted. Of the graduates, only 10 per cent were known to be dead, whereas 24 per cent of the partially rehabilitated had succumbed. The post-discharge work history was also decidedly more favorable for the graduates.

Some data on recurrences are given. It is stated that 12.5 per cent of the patients were discharged from the Camp as unimproved, nearly all of them being returned to a sanatorium for further treatment. This would appear to be a sizable proportion of reactivations among patients, most of whom had been out of the sanatorium less than one year. Yet the favorable mortality level and

subsequent work histories indicate that the recovery rate from such recurrences was high. Early detection of reactivation undoubtedly contributed to this. The statistics would have been more revealing, particularly for comparison with those of other institutions, had they been put on a person-year basis.

Mr. Holand's report will be especially useful to those concerned with the expanding field of rehabilitation. Lake Tomahawk State Camp is a unique project. Its organizational form was to a considerable degree geographically determined and probably it cannot be imitated very widely. But its success in terms of human values furnishes one more arrow in the quiver for the fight for a nation-wide rehabilitation program. With the publication of this history by the National Tuberculosis Association, another informative volume is added to an impressive shelf of books concerned with this subject.

E. ASHWORTH UNDERWOOD: *A Manual of Tuberculosis: Clinical and Administrative. Third Edition, largely rewritten. With an Introduction by Professor J. R. Currie. Pp. xvi + 524, with 88 illustrations, Williams & Wilkins, Baltimore, 1945, cloth \$4.50.*

By EMIL BOGEN

The fifteen years since the appearance of the first edition of this book have seen a revolution in our knowledge of, and our attitude toward tuberculosis, which is well exemplified in the changes which have been made in this rewriting. At times older conclusions which run counter to newer findings still persist, such as the conclusion that, "Every individual born and dwelling under ordinary conditions of civilization is infected after birth, and at some period between birth and the attainment of adult life with the tubercle bacillus," (p. 54); the statement that "at least 75 per cent of persons who have reached young adult life show that they have been infected in this way," (p. 44); and "By middle adult life 60 to 70 per cent of persons have been infected, according to the community," (p. 20). But in spite of such lags, the work as a whole reflects in an admirable way the latest information on the disease.

Although the volume includes almost every aspect of the disease which may be of interest to a physician, including the technique of artificial pneumothorax, pneumonolysis, thoracoplasty, Monaldi drainage, etc., it has been written also for the use of nurses, social workers and other intelligent laymen, so that the clarity of diction and simplicity of expression are remarkable, even among the English books which are noted for literary excellence. There are, of course, the inevitable typographical errors, (sever for severe, p. 191) which even the finest proof-reader is apt to miss, occasional chronological slips, such as making Pasteur a precursor of Villemin (p. 2), having the Royal Commission appointed in 1907 (p. 8), four years after it began its epoch-making studies, etc.

More culpable, perhaps, are the retention of obsolete concepts, such as the repeated references to an "envelope" protecting the tubercle bacillus (pp. 8, 158), to "toxins and toxemia" (pp. 86, 59) and their excretion (p. 159), living tubercle



bacilli in a fifth of calcified foci (p. 45), and particularly the inadequate standard of one bed per death (p. 442). Dissent might also be expressed to the recommendation of gold treatment in most instances in preference to bilateral or selective collapse (p. 235), to the recognition of pleural shock by the appearance of epileptiform convulsions (p. 247), to the emphasis on symptomatic classification of tuberculosis, ignoring the qualitative pathological groupings of Aschhoff and minimizing the radiological findings (p. 156), to the use of a fine needle for exploratory puncture of the chest for pleural effusions (p. 255), to the non-surgical treatment recommended for tuberculosis of the spine (p. 326), to the preference for 35 mm. rather than the larger size films for fluorography (p. 131), to the ignoring of the possibilities for eradication of bovine tuberculosis (p. 495), to the minimizing of the importance of bronchoscopy in pulmonary tuberculosis (p. 276), to the recommendation for extrapleural pneumothorax and Monaldi's cavity aspiration (p. 270), etc., but it is well to learn of the ideas of our British colleagues on these points.

The discussion of the effect of the war on tuberculosis, written before the war was over but already noting the return to prewar levels and analyzing the factors responsible for the early war-time rise in tuberculosis death rates, is of particular interest to those interested in the epidemiology of tuberculosis.

JOSEPH M. DOUGHERTY AND ANTHONY J. LAMBERTI: *A Textbook of Bacteriology and Immunology*. Pp. 360, The C. V. Mosby Company, St. Louis, 1946, cloth, \$4.50.

By MAX B. LURIE

This book is intended as an introduction for premedical students to bacteriology and immunology. The authors desire to inspire their readers with an enthusiasm for the subject.

In some respects, the writers succeed in their purpose. This is eminently true in their presentation of the early development of the sciences in the latter part of the nineteenth century. The elucidation of some serological phenomena, particularly of the complement fixation test, is accomplished with precision and clarity.

However, it is doubtful whether the authors have achieved their purpose of presenting to the young student the maximum impetus and allurements which is now implicit in these rapidly growing, intellectually stimulating and liberating sciences of bacteriology and immunology.

In the opinion of the reviewer, the difficulty lies in the concept of the authors that the chief interest of these sciences is their utilitarian values for public health, the diagnosis and treatment of disease. As a result, the book becomes a succinct catalogue of bacteria, protozoa and fungi and their implications in the practice of medicine and the control of contagious diseases. While these are undoubtedly important practical aspects of these sciences, they are far from being the only ones, or even the most significant ones from a cultural standpoint. Hence the

sweep of the larger concepts of the pure science of bacteriology is inadequately presented. Furthermore, the book suffers from a lack of treatment of the more recent, intensely fascinating advances in these sciences. Particularly, one misses the newer concepts in the field of chemotherapy. Little is said of Landsteiner's work on antigen-antibody relations and of the unlimited possibilities that have recently accrued from the study of these sciences as disciplines in pure biology and biochemistry. Because of failure to keep up with the newer knowledge, actual errors have crept into the text, such as the statement that proteins alone are antigenic, neglecting the demonstration that polysaccharides of bacteria can act in this capacity, particularly in man.

Another consequence of the utilitarian concept of bacteriology is the unduly large space devoted to mere technical procedures, such as the preparations of dilutions of sera and suspensions.

Here and there an uncanny moralizing note is heard, and apologia for mediaeval superstitions which appear out of place in a treatise of this nature.

To summarize, the authors present a simple statement of the highlights of the practical points of the old established bacteriology and immunology, but one rather misses the presentation of the surge of new knowledge and the growth of new fundamental principles, which are the chief fascination in the present-day sciences of bacteriology and immunology.

WILLIAM SNOW: *Principles in Roentgen Study of the Chest*. Pp. ix + 414, with 508 illustrations, 1946, Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Illinois, fabrikoid, \$10.00.

By L. H. GARLAND

This book consists largely of a collection of roentgenographic reproductions with legends of variable accuracy.

The text contains many statements which must be regarded as not only new but positively startling. On page 19, the author notes that "Bronchial spasm, carbon dioxide tension and the lung circulation are tied together." On page 354, he inquires, "Is it not possible that Metchnikoff was correct in the use of bacillus bulgaris (sic) in buttermilk for increased longevity?"

Many of the illustrations are unduly dense or fogged in their upper halves. The legends are not always entirely logical; for example, figure 276 might well be sarcoidosis and not leprosy.

The work is not recommended for either students or practicing physicians.

### *Brief Comment*

HENRY D. CHADWICK AND ALTON S. POPE: *The Modern Attack on Tuberculosis*. Revised Edition. Pp. viii + 134, New York, The Commonwealth Fund, 1946, cloth, \$1.00.

Since this book was first published in 1942, it has gone through three reprintings and now a revised edition is presented. This great demand is a more telling proof of its usefulness than any laudatory review could be. In this revised edition,

the reader is brought up to date, as the authors state in the preface, "on the many recent developments in administrative practice and in the techniques of tuberculosis case-finding and control; it includes a new section on pathogenesis and a detailed discussion of the predisposing factors to the development of tuberculosis. New material has been added and various sections have been expanded to include: photofluorography and the rôle of mass X-ray examinations in industry and other population groups, with emphasis on the essential rôle of the organized follow-up system; the financial aspects of hospitalization; rehabilitation; chemotherapy; immunization; and the Federal case-finding program."

These additions do not only modernize this manual, but they contribute in an important manner to a better understanding of the problem. The bibliography has been expanded in accordance with the newly added topics.

How rapidly the development of our knowledge in tuberculosis increases, is indicated by the fact that this revised edition does not as yet include a discussion of negative tuberculin reactors, who have roentgenologically demonstrable calcifications in lung and mediastinal lymph nodes; nor the tentative conclusions which have been reached concerning sensitivity to histoplasmin in such persons. This and other new developments will unquestionably demand further revised editions, at decreasing intervals, of this well written and most informative book.

## AMERICAN TRUDEAU SOCIETY

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\* Executive Committee.

<sup>1</sup> Died November 25, 1946.

## *AMERICAN TRUDEAU SOCIETY*

The Council of the American Trudeau Society announces with deep regret the death of eighteen of the Society's members during the year 1945-1946:

Vitaly J. Alexandrov, M.D., Rutland, Massachusetts  
Osbourne O. Ashworth, M.D., Richmond, Virginia  
F. Herbert Bartlett, M.D., Muskegon, Michigan  
Walter Baumgarten, M.D., St. Louis, Missouri  
William Frederick Bennett, M.D., Verona, New Jersey  
Bascomb Lanier Chipley, M.D., Chillicothe, Ohio  
Benita C. Davenport, M.D., Middleboro, Massachusetts  
Charles J. Dietrich, M.D., Reading, Pennsylvania  
Louis Hamman, M.D., Baltimore, Maryland  
Fred H. Heise, M.D., Saranac Lake, New York  
Clarence L. Hyde, M.D., East Akron, Ohio  
John Dee Jackson, M.D., Kerrville, Texas  
Ralph C. Matson, M.D., Portland, Oregon  
John D. McLean, M.D., Philadelphia, Pennsylvania  
Charles W. Mills, M.D., Tucson, Arizona  
Philip H. Pierson, M.D., San Francisco, California  
Herman H. Schultz, M.D., Ingleside, Nebraska  
B. A. Shepard, M.D., Oshtemo, Michigan

## AMERICAN TRUDEAU SOCIETY

### Report of the 1946 Annual Meeting of the California Trudeau Society

The California Trudeau Society had its annual meeting in joint session with the California Tuberculosis and Health Association, in San Francisco, April 22, 23 and 24, 1946.

The Society has 208 active members at this date. Officers elected for the coming year are:

President, Bruce Steel, M.D., Santa Barbara  
President-Elect, Cabot Brown, M.D., San Francisco  
Vice-President, Jane Skillen, M.D., San Fernando  
Secretary-Treasurer, C. Gerald Scarborough, M.D., San Jose

The first meeting was in joint session with the Administrative Section of the California Tuberculosis and Health Association. William P. Shepard, M.D., the President-Elect of the National Tuberculosis Association, presided. Wilson L. Halverson, M.D., Director, California State Department of Health, discussed *Facts for Action*. He summarized the Emerson report as it applies to California. It showed that our ageing population is a real public health problem and discussed the relation of heart disease, cancer control, accident prevention with regard to the public health program of California. He concluded with the statement that we should lay plans on all health fronts while attacking the pressing problem of the moment.

Louis I. Dublin, Ph.D., of New York, discussed *The Future Role of Voluntary Agencies*. He compared the present situation with that at the time when he discussed a paper on a similar topic in 1923 before the annual meeting of the National Tuberculosis Association in San Francisco. He pointed out that six States now have a tuberculosis mortality rate of less than 20 per 100,000, and that we should consider, at this time, trends in tuberculosis and the future use of Christmas Seal Sale funds. The Association should be ready to take a broad view of the place of the Tuberculosis Association in the public health program as a whole. In the past, the tuberculosis campaign has frequently had to make adjustments of programs to the progress of conditions. The official Public Health Agencies have taken over and expanded a good deal of the tuberculosis program from the public health standpoint, in accordance with plans sponsored by the National Tuberculosis Association. We now have Federal and State Departments devoted entirely to tuberculosis. They have taken over many of the functions of the voluntary agencies. He compared San Antonio, Texas with Syracuse, New York, and stated that in 1945 San Antonio had a tuberculosis death rate of 100, needed clinics, beds, contact examinations. These were fundamental needs which had not been met. He also pointed out they had a very low Seal Sale per capita. Syracuse, New York, on the other hand, with a tuberculosis death rate of 30, besides having an adequate tuberculosis program, had

embarked into heart diseases, child-care, cancer and a broad public health program, and this area had a high Seal Sale per capita. The local Tuberculosis Associations should adapt their programs to the local needs. He stated that the Tuberculosis Association is not a professional medical society, but that these are public institutions and their policies should be dictated by the public. He advocated a restudy of the relations of the National Tuberculosis Association to other health agencies and to the National Health Council. Some of the further work of the Tuberculosis Association must be broadly based. We will get more and more money and have less to do, so the program that develops must be realistic.

H. Corwin Hinshaw, M. D., Associate Professor of Medicine at the Mayo Foundation, Rochester, Minnesota, discussed *The Medical Future of Tuberculosis Control*. He felt that the rôle of the general practitioner is important in tuberculosis control. It is the function of the physician to see that the personal problems of the individual patient are solved. Diagnosis is his particular sphere and this applies to tuberculosis as well as other diseases. Surveys are necessary and important and are useful also as pointers to find open cases, and these should include the follow-up of known contacts. An exclusion test for tuberculosis should be generally performed by every physician, either tuberculin tests followed by X-ray examination of the reactors or, perhaps better yet, the routine X-raying of all patients regardless of complaints. The general practitioner should use these procedures as he has learned to use urine tests, the Wassermann reaction and the routine determination of blood pressure. X-ray films of the chest are becoming routine in preoperative patients and in all prenatal examinations. X-ray examination of the chest frequently does not yield a specific diagnosis but is certainly the first, and may be the most important step, in obtaining one. Routine chest X-ray films on all hospital admissions are becoming more widely used and this procedure protects the hospital employees as well as other patients from contagion. It is probable that in the future accredited hospitals will be expected to take routine chest roentgenograms of all patients.

The teaching of tuberculosis could be improved in many medical schools, and here special emphasis should be given to the chest X-ray examination as a method of physical diagnosis. The treatment of active tuberculosis should be done by a specialist and not by the general practitioner. Many patients, however, after sanatorium care must of necessity return to the general practitioner who must be better informed as to proper care of latent tuberculosis. Thoracic surgery has become the most important therapeutic procedure in tuberculosis and there is an inadequate supply of well trained thoracic surgeons. In some locations sanatorium beds are kept filled for unduly long periods of time with patients whose sanatorium care could be shortened if surgery were available to them.

More research is needed in tuberculosis. This should have priority in funds. Research may often give negative results, but these are not to be minimized. One should not confuse discovery with research, as discovery may be only a fortunate accident. Chemotherapy has vast possibilities but has been very in-

completely studied. If it will only cut down the time required to render a patient's sputum negative, we could greatly increase the use of our present bed capacity. There is no chemotherapeutic remedy on the horizon that will accomplish the marvels for tuberculosis which parallel the accomplishments of penicillin in pneumonia. With particular regard to streptomycin, these facts are known:

1. Tubercle bacilli cannot grow in the presence of this antibiotic.
2. Infected animals have their life prolonged perhaps indefinitely (guinea pigs and mice).
3. Tubercles are profoundly modified and may be eradicated in experimental animals.
4. It can be given to patients for prolonged periods with reasonable safety.
5. Patients have frequently improved under this therapy but the clinical possibilities and limitations of the drug are not fully explored.
6. It is not a rapidly curative drug; it does not kill tubercle bacilli but does inhibit their growth.
7. If the treatment with streptomycin is interrupted, tuberculosis sometimes recurs.

Doctor Hinshaw closed by saying that we do have a tuberculosis problem. We have the weapons, but they must be employed on a much greater scale if we are to control this disease. Research can improve these weapons. Tuberculosis complicates so many other diseases, that the general physician, in average practice, cannot afford to neglect X-raying the chest of all patients regardless of complaints.

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On Wednesday, April 24, the meeting continued with the general topic of *Evaluation of Therapy and Control Measures in Tuberculosis*, C. Gerald Scarborough, M.D., Chairman.

At this time, Doctor Hinshaw discussed the evaluation of chemotherapy in tuberculosis. He showed how the experimental work with promin permitted the development of a method of evaluation of chemotherapeutic agents. Animals were infected with tubercle bacilli and several weeks later these infected animals were examined by laparotomy, biopsies being taken particularly from the liver before treatment was started. Thus, one had an opportunity to compare the appearance of lesions in the same animal before and after treatment. The life of guinea pigs was greatly prolonged by the use of promin and, in one experiment cited, 87 per cent survived 220 days under treatment, whereas 100 per cent of the controls were dead by that time. Proved lesions of the liver have been known to disappear. Many similar compounds of the sulfone series of drugs have been studied but none were found to be superior to promin.

Turning to antibiotics, he stated that a number of substances of microbial origin have been tried in tuberculosis since 1883. The most promising antibiotic is streptomycin. In one experiment 49 guinea pigs were infected with tuberculosis and, seven weeks later, treatment was started. After five and one-half months of treatment there was very little evidence of tuberculosis in these animals. In this experiment, 9 of the treated guinea pigs did not react to tuberculin after treatment, although they had previously reacted. Emulsions of their



spleens did not cause tuberculosis on animal injections. In comparing various drugs, the sulfonamides have slight effect *in vitro* and are but weakly effective *in vivo*. Penicillin is ineffective against tubercle bacilli; promin, diasone, etc. are effective against tuberculosis in guinea pigs, but are poorly tolerated by humans. Streptomycin is well tolerated by humans. From observations on 63 patients with tuberculosis treated with streptomycin, it was concluded that there was consistent improvement and that no lesions progressed during treatment, but occasionally there was prompt return of the lesions after treatment was stopped.

Streptomycin does not penetrate into the brain substance and some patients with miliary tuberculosis developed a peculiar type of tuberculous involvement of the brain substance when the disease was inhibited elsewhere after treatment with streptomycin. On pathological study, an anatomical picture was presented which had not been previously seen.

After a few months of streptomycin treatment an acquired resistance of organisms to streptomycin has been observed. The clinical significance of this is not yet known. The toxicity of streptomycin is greater than that of penicillin but less than that of the sulfonamides. The vestibular branch of the eighth nerve or its end organ is definitely affected in some patients. At the present time streptomycin is allocated by the National Research Council, and its availability is very limited. The next step recommended in this program, when production permits, is the establishment of several parallel clinical research projects.

Benjamin L. Freeland, M.D., reported on *Chemotherapeutic Research*. This investigative work is being carried on in San Francisco under the joint auspices of the National Tuberculosis Association, the California Tuberculosis and Health Association, the San Francisco Tuberculosis Association and the Columbia Foundation.

In the search for new chemotherapeutic agents one does not proceed entirely by the empirical method, in which all types of chemicals are tested. There are many factors in the evaluation of new chemicals which determine in advance whether a compound is worthy of further investigation. These include the following:

1. *Toxicity*: Highly toxic substances and protoplasmic poisons are ruled out.
2. *Absorption*: Insoluble compounds are unlikely to be absorbed; the compound must be soluble in either water or lipids.
3. *Transport*: After absorption the chemical must be carried by the blood and remain relatively unchanged until it reaches the focus of infection. A large number of compounds are changed or destroyed as they pass through the liver.
4. *Cell penetration*: The penetration of the bacterial cell by a compound may depend upon:
  - (a) The hydrogen ion concentration of the cell and the surrounding medium.
  - (b) The degree of ionization of the compound.
  - (c) The water-lipid solubility ratio. The cell surface of the tubercle bacillus is highly resistant to inorganic acids, as well as to compounds, in general, in a highly ionized state. On the other hand, there is reason to believe that the

intracellular susceptible enzyme system is more affected by compounds in the ionized state. It is asking much of a new therapeutic agent, to have it remain un-ionized until it passes the cell surface, and then have it become ionized.

There are three further rigorous screening tests, which a new therapeutic agent must pass in order to be effective. They are as follows:

1. High bacteriostatic effect *in vitro*, in the presence of serum.
2. The concentration of the compound which is bacteriostatic should be less than the concentration which injures leucocytes.
3. The chronic toxicity of the compound in animals must not be too high. Of the thousands of surface germicides, which have been reported, there are not ten which are less toxic to the host than to the parasite. Florey has postulated that the beneficial effects of penicillin depend on the simultaneous action of the leucocytes and other defense mechanisms, which deal with the bacteria, while multiplication is held in check by the penicillin. In the therapeutic evaluation of new chemicals, there is a prevalent illogical tendency to push the dosage to tolerance, without consideration of the toxic effects of these drugs on other defense mechanisms.

We have synthesized various new derivatives of diphenylsulfones, sulfoxides and sulfides; and have tested their effects *in vitro* and *in vivo*.

*Sulfones*: 2,4'-diaminodiphenylsulfone; 2,2'-diaminodiphenylsulfone; 4-benzylideneamino 4'-aminodiphenylsulfone; 4-nitro 4'-acetylaminodiphenylsulfone; 4-iodo-4'-aminodiphenylsulfone.

*Sulfoxides*: 4,4'-diaminodiphenyl sulfoxide; 4,4'-diacetylaminodiphenyl sulfoxide; 4-nitro 4'-aminodiphenyl sulfoxide; 4-iodo 4'-aminodiphenyl sulfoxide.

*Sulfides*: 4 chloro 4'-aminodiphenyl sulfide (also acetylated); 4-iodo 4'-aminodiphenyl sulfide.

The 2,2' and the 2,4'-diaminodiphenylsulfones were less bacteriostatic than the corresponding 4,4' derivative. The diaminodiphenyl sulfoxides show approximately the same inhibitory effects *in vitro* and *in vivo*, as the corresponding sulfones. The 4-benzylideneamino 4-aminodiphenylsulfone shows the same therapeutic effect in animals as the parent compound; it probably hydrolyzes to diaminodiphenylsulfone in the body. The halogenated sulfides inhibited the growth of tubercle bacilli *in vitro* in very high dilution (1:800,000); however, they were highly toxic and showed no therapeutic effect *in vivo*. The sulfoxides, like the sulfones, were antagonized by p-amino benzoic acid; the halogenated derivatives were not.

Robert J. Anderson, M.D., Chief of the Bureau of Tuberculosis, State Department of Health of California, discussed *The Evaluation of Control Measures in Tuberculosis*. He cautioned against the use of mortality rates alone as an index of effectiveness of our tuberculosis program, citing areas of no tuberculosis program with low mortality and areas of good tuberculosis programs with high mortality. Housing and the standard of living must be considered as having some inverse relationship to the extent of tuberculosis. With regard to case-finding tuberculin tests are useful when the rate of infection in the population is low.

In younger age groups, it can be used as a pointer to the index case. With mass X-ray studies, it is theoretically possible to X-ray yearly all the population in the United States. Case-finding by this method does not mean diagnosis. There is not a very significant difference, at the present time, between various types of miniature films in picking out those cases necessary for further study. What we are really looking for here are those cases that have positive sputum and those lesions that can be effectively treated. X-raying older age groups on routine hospital admissions is particularly important. A special X-ray set-up was not economical in hospitals with less than 75 admissions per day. If there were 25 admissions a day, it would be just as well to use the present X-ray facilities using large films. The cost in the long run would not be much different. One should also have good clinic service. The clinics would serve the known contacts and the patients with symptoms, while surveys in general would find the index cases. Thirteen per cent of cases in California last year were not reported before death. A few counties, mostly smaller ones, had no cases reported before death. In four counties there was excellent reporting. Kern, Orange, Sacramento and San Francisco had 5 per cent of tuberculosis deaths not previously reported. There should be close coördination between the hospital and the Health Department.

The Public Health Nurse must choose which cases to follow to make her work effective. The standard of one nurse to every 5,000 population is seldom met. She should, therefore, pick out those cases who first have positive sputa; second, the recent sanatorium discharges; and, third, newly diagnosed cases. Rehabilitation is an important tuberculosis control measure.

Louis D. Martin, of Los Angeles, reported on *Heart Findings in Mass Surveys*. He stated that while X-rays are much more effective in finding tuberculosis than the stethoscope, this is not true of heart lesions. However, heart lesions of certain kinds can be found upon all types of X-ray films of the chest. Changes in technique of taking chest films affect the heart findings. In a study of 63,398 miniature films taken in Los Angeles in industry, over the past three years, 2.7 per cent showed tuberculosis and 2.0 per cent showed heart abnormalities. These were not checked clinically for their heart lesions as a routine matter. In another study of 8,000 miniature chest films, 414 had abnormalities of the heart or lungs and 151 of these showed heart lesions; 77 per cent of these were reëxamined. There was 75 per cent clinical confirmation of the heart X-ray diagnosis, one-half of these cases being newly discovered. This group, of course, is not representative of all the adult population, as they were all workers.

Gross abnormalities of the size and shape of the cardiac shadow is easily recognized. Lesser changes require measurement. An attempt was made to find a factor that could be applied to miniature films to use in detecting cardiac abnormalities. These were divided into those showing small enlargement, average, slight, moderate and gross. One hundred and ten very carefully worked-up cases were studied using standard film at 72 inches, 4 x 5" at 43", and orthodiagrams. These films were all taken on moderate inspiration. Forty-three were

repeated on expiration and showed a marked variation of 27 per cent difference between inspiration and expiration; 5 per cent of the cases could not be measured accurately due to motion or pericardial fat. Large films, however, present the same difficulty. A 3.7 conversion factor was found. If the 4 x 5" measurements were multiplied by this, the variation should not exceed 10 per cent over the Ungerleider standard. The ratio of the cardiac diameter to the chest diameter showed less than 2 per cent difference in the various methods outlined above, in 75 per cent of the patients. The difference in the rest was less than 5 per cent variation by these three different methods. The method, therefore, was 93 per cent accurate in determining cardiac enlargement. If this is used in routine surveys the patients weight and chest measurement must be added to the survey. Applying these standards, of course, would greatly delay film reading, as careful measurements must be done. He concluded that this study shows that small films are as reliable as any other method of determining heart size, when the above factors are taken into consideration.

Charles E. Smith, M.D., Professor of Public Health and Preventive Medicine, Stanford University Medical School, San Francisco, gave a *Progress Report of Coccidioidomycosis Research*. There were established, in California and the Southwest, Service Camps with large groups of men. Their presence required the critical reevaluation of the facts in this disease. In general, the previously known facts have been substantiated. In one study it was found:

Total number of infections . . . . .	1,163
Diagnosed cases . . . . .	23.2 per cent
Missed and subclinical cases . . . . .	16.8 per cent
Inapparent infections . . . . .	60.0 per cent

Of the diagnosed cases, 18.2— showed erythema nodosum or multiforma, and 4.2 per cent of all the cases.

In white patients, there were 1,061 males (4 per cent) who showed erythema nodosum and 28 females (25 per cent) who showed erythema nodosum. There was a marked racial difference in the distribution of disseminated coccidioidomycosis in males. There were 11 such cases in Negroes, or 2.5 per cent of the infected ones; whereas, there was only one case in the whites, or 0.25 per cent of the infected ones.

Seasonal rainfall markedly affects the infection rate, showing it is air-borne and dust-borne, a characteristic of the disease. This cycle repeats itself yearly; dust control, therefore, in these camps is very essential to prevent infection in the dry season. Africa, Australia and the Near East seem to be free of the disease. It is present in West Texas. In Central Arizona there is 60 per cent infection; in Phoenix and Tucson, less. In California, the Southern San Joaquin Valley is an area of high infection; further North infection decreases. There is an infected area along the Southern Coast of California around Riverside and Banning, and in Southern Utah, and Southern Nevada. Particular caution is necessary to prevent laboratory infections. The culturing of the organisms is very hazardous as

they dry. By such exposure extremely severe infections are caused. The coccidioidin skin test is very valuable but not as easy to interpret as the tuberculin test. It is important that new syringes and needles be used and that the injections be intracutaneous. Sensitivity to coccidioidin may be slowly lost. In a 1:100 dilution the coccidioidin remains potent for at least one year in a refrigerator, if kept uncontaminated. If undiluted, it remains fully potent for at least seven years. Streptomycin has no effect upon coccidioides infection.

Richard C. Smith, M.D., Director of the Laboratory, Barlow Sanatorium, Los Angeles, presented a study on *Air-borne Infections in Tuberculosis*, in collaboration with John H. Urabec and J. Lloyd Mason. In discussing droplet infections, it is shown that these droplets can contain tubercle bacilli but most of them are not fine enough to penetrate into the lungs. Dust from bed-making and sweeping may carry tubercle bacilli and is capable of reaching the pulmonary alveoli. The work of Wells and Wells, in 1936, was reviewed showing that droplets can evaporate giving dry nuclei containing bacteria that are readily breathed into the lungs. Some die in an hour or so, but tubercle bacilli may survive a much longer period. At Barlow Sanatorium, no tubercle bacilli were found in the sweepings from the floor, bed-side furniture and books. Unfiltered north light kills tubercle bacilli in a few hours. Petri dishes in tuberculosis patients' rooms showed 87 per cent infection after a week, according to Pressman. Bogen, using a similar procedure, found only 5 per cent of such Petri dishes positive, and these only in the Admitting Room and the Laboratory. At Barlow it was rare to get tubercle bacilli directly from the air. There have been many studies in air-borne infections, other than tuberculosis, in recent years. The effects of air-conditioning, ultra-violet, oiling floors and bed clothes, glycol vapor, and the effect of ventilation alone were discussed.

Using the Pressman method for collecting the settling dust, at Barlow Sanatorium they did 26 tests using 97 Petri dishes—7 in the laboratory and animal house and 19 in hospital rooms. They were all negative for tubercle bacilli. Several other acid-fast bacteria were found, however.

The same type of tests was done in the tuberculosis wards of a large general hospital:

Total tests.....	17
Dishes set out.....	95
Wards tested.....	22
Patients in rooms.....	239
Positive results.....	3

Air filtration tests (Barlow Sanatorium) were carried out as follows:

Rooms tested.....	7
Hours of run of the air test apparatus, average ...	15
Cubic feet of air per test.....	723
All were negative by animal inoculation and culture.	

At Barlow Sanatorium a series of tests were done by atomizer—bubbler technique:

Rooms tested.....	5
Average hours per run.....	6
Cubic feet of air per test.....	53
All were negative on culture and animal inoculation.	

We do not yet understand exactly how tuberculosis is transmitted. The findings for other air-borne diseases indicate that a large share of infection in tuberculosis occurs via the air. We need better methods of isolating tubercle bacilli from the air to prove or disprove this.

Sidney Raffel, M.D., Associate Professor of Bacteriology, Stanford University School of Medicine, Palo Alto, discussed *Immunity Research*, which he had been carrying on for several years with the aid of grants from the Committee on Medical Research of the California Tuberculosis Association and the National Tuberculosis Association. He felt that a major goal was to correlate the clinical and pathological findings with the constituent parts of the organism, not only in tuberculosis but in many other diseases. Many of the major fractions of the human tubercle bacillus have been studied, such as the proteins, the carbohydrates, the phosphatides and the waxes.

In laboratory animals, it has been possible to reproduce hypersensitivity, antibodies and tissue reactivity to isolated substances of the bacillus, but acquired immunity has not, to this date, been reproduced with a chemically separated antigen. An attempt is being made to derive complexes to reproduce this reaction. A study was made of what happened to animals which were desensitized completely to tuberculin. It was concluded that their immunity remained intact, though use of Old Tuberculin in large doses for this purpose was deleterious in general for these animals. Using the pure unheated protein from the tubercle bacillus, the same results were obtained but the animals were in much better general condition.

Fourteen cases of Boeck's sarcoidosis were studied for their humoral response. These did not show the antibody distribution seen in cases of tuberculosis, in which 90 per cent revealed a characteristic pattern. The distribution of antibody in this series of sarcoidosis was like that in the general population. This study is being continued, but it adds indirect evidence for the fact that there is no relation between tuberculosis and sarcoidosis.

On the afternoon of the 24th, a *Symposium on the Evaluation of Surgical Procedures* was held, under the Chairmanship of Joseph L. Robinson, M. D., of Los Angeles.

The first presentation was by Jerome R. Head, M.D., of Chicago on *Evaluation of Surgical Procedures*. Doctor Head presented a summary of present-day concepts of the usefulness of various types of surgical collapse in pulmonary tuberculosis. He felt that his impressions were formed not through statistics alone, but by clinical experience with a large number of patients. He felt that collapse was almost specific treatment for tuberculosis and that with adequate collapse most patients will get well. Strict bed-rest is the basic treatment and may at times be the only treatment necessary. Small doses of X-ray for obviously en-

larged mediastinal lymph nodes are used. Early lesions in adults are now found that are primary infections with glandular enlargement. Early phrenic interruption in unilateral cases, especially with cavities near the hilum, may be helpful. Phrenic interruption in lower lobe involvement may not help. He uses a period of initial bed-rest of four to five months before starting pneumothorax. He believes that in the long run this may save time and result in early working efficiency. He uses a phrenic operation often when reexpanding a lung following pneumothorax. Patients with bronchial stenosis should be immediately collapsed or that portion of the lung removed. He advocates early thoracoplasty for acute cavities, even if the patient is very toxemic, if other measures are not promptly effective. There was much to be said in favor of thoracoplasty against pneumothorax, but in general he uses thoracoplasty only when pneumothorax has failed or is not advisable. He advised early collapse and early return to work.

Internal pneumonolysis was used only for suspended cavities or persistently positive sputum. Results of stomach content examination are too delicate a test for clinical tuberculosis regarding the effectiveness of treatment. Sometimes a small apicolysis is valuable, but a large one should be condemned because too much effective lung tissue is sacrificed. Usually six or seven ribs were removed in thoracoplasty and the tip of the scapula was transplanted into an extrapleural pocket instead of resecting it. Large apical cavities are always difficult to collapse and an occasional paraffin pack is used. Occasionally the Monaldi technique followed by a thoracoplasty is effective in difficult types of cases where other methods are not applicable.

With regard to bilateral pulmonary tuberculosis, one must clearly differentiate whether these are bronchogenic and therefore acute problems, or hematogenous and therefore slow and chronic. The latter have many extrapulmonary complications. With a bronchogenic spread, a long period of initial bed-rest is recommended and late collapse, if possible. With the hematogenous type, tubercle bacilli are hard to demonstrate. Many times these are called "inactive" on insufficient evidence. They show slow spread with few symptoms over a period of many years (ten to fifteen years). They are resistant to treatment, but they can be arrested by pulmonary collapse. One may have to use bilateral thoracoplasty or extrapleural pneumothorax may be indicated. With extrapleural pneumothorax one should give a little more collapse than is necessary and then allow it to retract to fit the size of the lesion, converting the extrapleural pneumothorax to oleothorax at a later date. The collapse in these cases should be toward the mediastinum and not down from the apex.

One may do a paraffin pack occasionally before doing a thoracoplasty in apical cavities with hard apical lesions. Many of these develop complications but the complications are rarely fatal. They are bothersome but can usually be controlled. Paraffin pack is the method of choice in the older group of patients. Bronchial tuberculosis was discussed with reference to lung resection. This type of lesion produces early and extensive spread. Patients showing ulcerative tracheo-bronchial lesions only, can be more readily controlled by treating the

lung lesion itself. Bronchial disease with stenosis, tuberculoma, basal cavities, may be suitable for lobectomy. It is still open to question whether this is a better method than slower types of collapse. Doctor Head concluded that each procedure had its own use, and when cases were properly selected, each procedure may contribute something to curing these patients.

*War Surgery of the Chest* was discussed by Paul C. Samson, M.D., of Oakland, Chief of Thoracic Surgery of Alameda County Institutions. He was interested, particularly, in its practical application to civilian problems. He saw 1,000 chest wounds and reviewed 4,500 records. Ten per cent of the casualties had some type of chest wound, two-thirds of these penetrating.

World War I had a 50 per cent fatality in patients with penetrating wounds that reached the hospitals. Of the present group studied, there were 1,700 penetrating wounds of the chest with a 9.9 per cent fatality. Those where the primary chest wound was the most important wound gave 4.3 per cent fatality. Thoraco-abdominal wounds are serious complications. Anesthesia, chemotherapy, better technique, the increased use of blood and the treatment of shock contributed toward this remarkable improvement. Patients who are in marked shock should be left alone as far as the wound is concerned and, as far as possible, the shock should be controlled. This may delay surgery up to forty-eight hours. Not too much fluid should be given and not too rapidly. Blood and plasma were used extensively but not too much crystalloid solution. Blood should be given to replace only the blood loss.

It was important to control thoracic pain. This was done by intercostal nerve block. These chests should not be immobilized with adhesive. Regional block at the angle of the ribs allows the cough reflex to function and results very quickly in complete relief. It is useful in fractured ribs, pleurisy, herpes, and lasts about twenty-four hours.

The "wet lung syndrome" was discussed. It results from hemorrhage of the lung, causing edema, fluid in the alveoli and smaller bronchi, wheezing, ineffective cough and respiratory decompensation. The treatment was to maintain an adequate airway and get the bronchi clear by controlling pain with nerve block to allow coughing and by mechanical suction by bronchoscopy or catheter aspiration.

The latter was used extensively, using a 16-gauge catheter, no anesthesia and electric suction. The catheter should be passed through the nostril with the head forward and the tongue pulled out; as it enters the trachea, the patient coughs severely. Suction is applied from three to five seconds after the catheter is in place. The catheter goes easily into the right bronchus. When the head is turned to the right, it can be gotten into the left bronchus. This type of suction is very effective and can be repeated hourly, if necessary.

There were 60 cases of cardiac lesions, 30 per cent showing contusion of the heart muscle. Surgery in these patients should be delayed for at least twenty-four hours. Transpleural exposure of the heart was found most satisfactory, extrapleural approach not being practical.



Cardiotomy for the removal of missiles is a practical procedure. With pressure pneumothorax, in emergency a needle or a needle plus a tube and a water trap may be used. This is not suitable for transportation. Instead a catheter is used, 20 or 22 gauge. The caliber of the catheter should be larger than the tear in the lung. The use of a finger cot with a slit over the end for transportation is especially useful in spontaneous pneumothorax.

In hemothorax air replacement was found to be bad. Early and frequent aspirations did not increase bleeding. Where extensive clotting occurs (as it did in 10 per cent of the cases) infection is favored. Frequent aspirations are recommended, if they are possible. A decortication operation is very effective if done early (after a few weeks). The lung expands well and the function will be approximately normal. The X-ray shadow in these cases usually is not due to a thickened pleura but to a heavy organized membrane that can be peeled off leaving normal pleura. The fatality from this procedure is about 1 per cent.

Two papers were presented on the current status of formerly popular procedures. Ambrose Churchill, M.D., of Los Angeles discussed *Extrapleural Pneumothorax*. A group of 25 patients operated in 1937 and 1938 showed: 50 per cent cured; 30 per cent dead; 20 per cent still active; 4 were still getting air; 9 have oleothorax; 1 has had a thoracoplasty; in 11 the pocket is obliterated. Half of these patients are working a full day.

Alarcon's figures from Mexico show similar results. This procedure still has a definite place in a few selected cases.

Lyman Brewer, M.D., of Los Angeles, discussed *Wax Plombage*. He felt that improvement in thoracoplasty technique has greatly reduced the necessity for plombage. Some of the former indications have been replaced by extrapleural pneumothorax. His group has done no primary plombages recently, but to close the cavity following an unsuccessful thoracoplasty this method has a definite place.

HAROLD GUYON TRIMBLE

## AMERICAN TRUDEAU SOCIETY

Postgraduate Course in Thoracic Diseases  
University of Wisconsin Medical School, Madison, Wisconsin

March 3 to 8, 1947

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A Postgraduate Course in Thoracic Diseases sponsored by the American Trudeau Society in coöperation with the University of Wisconsin Medical School will be given March 3 to 8, 1947, at Madison, Wisconsin. (Printed copies of the program for prospective students will be obtainable from the American Trudeau Society, Cameron St. C. Guild, M.D., Executive Secretary, 1790 Broadway, New York 19, New York.)

This intensive course is made available at minimum cost by the Society, which assumes full responsibility for promotion, advertising and registration.

*Registration:* Maximal registration—30. This course is intended primarily for physicians residing in the following states: Ohio, Indiana, Michigan, Illinois, Wisconsin, Missouri, Iowa and Minnesota, although applicants from other areas will be given due consideration.

Applicants should write to Cameron St. C. Guild, M.D., Executive Secretary, American Trudeau Society, 1790 Broadway, New York 19, New York, request-ion blanks. Notification of acceptance will be made by February first.

*Fee for course:* Fifty dollars. Checks should be made payable to *The American Trudeau Society*.

## *NATIONAL TUBERCULOSIS ASSOCIATION*

### **Director of Research**

October 21, 1946

Appointment of Dr. Esmond R. Long, Director of The Henry Phipps Institute for the Study, Treatment and Prevention of Tuberculosis, Philadelphia, Pennsylvania, to the post of Director of Research of the National Tuberculosis Association was announced to-day by Dr. William P. Shepard, San Francisco, President of the N.T.A.

Doctor Long was chief consultant on tuberculosis in the Office of the Surgeon General of the Army from July, 1942 to March, 1946 with the rank of Colonel. During November and December, 1945 he served as acting director of the Tuberculosis Service of the Veterans Administration. He continues to serve as tuberculosis consultant to the Army and Veterans Administration. He is also a tuberculosis consultant to the U. S. Public Health Service. He was president of the N.T.A. in 1936-1937 and has been a member of the Committee on Medical Research since 1929.

Originator of "Long's Medium," a synthetic medium for the growth of tubercle bacilli, Doctor Long received the Trudeau Medal for tuberculosis research in 1932. He has been engaged for many years in studies on the nutrition of the tubercle bacillus and the chemistry of tuberculin. He is a member of the National Academy of Sciences.

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